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Editor
ROY WALDO MINER

THE STATUS OF MULTIPLE SCLEROSIS

BY

PEARCE BAILEY (*Conference Chairman*), HAROLD R. WAINERDI (*Organizing Chairman*), H. A. ABRAMSON, L. ALEXANDER, O. E. BUCKLEY, L. D. BUNCH, B. CAMPBELL, G. G. DEAVER, C. R. FRANKLIN, L. W. FREEMAN, G. H. GLASER, S. S. GOLDENSOHN, P. J. HARMAN, M. HARROWER, C. HERRMANN, JR., R. R. HOWARD, H. H. JONES, H. H. JONES, JR., E. A. KABAT, S. S. KETY, L. T. KURLAND, M. MARKS, H. H. MERRITT, J. MOLDAVER, W. P. PARKER, E. PASTORE, A. M. RABINER, A. SAIFER, I. M. SCHEINKER, G. A. SCHUMACHER, A. SHAPIRO, R. E. STAUFFER, E. TEIGE, N. TELLES, B. W. VOLK, B. H. WAKSMAN, B. S. WALKER, K. B. WESTLUND, AND M. D. YAHR.

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INTRODUCTION

By O. E. Buckley

Chairman, Board of Directors, National Multiple Sclerosis Society

The problem treated in this monograph is of such magnitude as to cause wonder that so little is presently known about the cause and nature of the baffling disease known as multiple sclerosis. As you know, it has been estimated that there are from 200,000 to 300,000 cases of this malady in the United States. Recent studies have shown that the survival of multiple sclerotics is much greater than was once thought to be the case and, indeed, their over-all life expectancy approaches that of the population as a whole.

Multiple sclerosis has its highest incidence in the third and fourth decades of life, does not apparently tend to favor one sex as compared to the other and, contrary to what has been thought in the past, does not attack any particular racial or national group. One solid, well demonstrated fact is that within the temperate zone of North America, this disease is much more common in the northern latitudes than in the southern. Whether this fact holds true for the temperate zone areas in the other continents is not presently known, and, indeed, one can only speculate about the number of cases which exist in the world. Careful studies in this connection remain to be made.

It is with great personal satisfaction that I have seen this Conference, on which this monograph is based, develop, and I gratefully acknowledge the indebtedness of the National Multiple Sclerosis Society to The New York Academy of Sciences, particularly to Mrs. Miner and her colleagues, whose expert guidance has been invaluable to Doctor Wainerdi, the Organizing Chairman.

On behalf of the National Multiple Sclerosis Society I wish to acknowledge the cooperation of those who have joined in making the Conference a success.

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Conference Chairman: PEARCE BAILEY
Organizing Chairman and Consulting Editor: HAROLD R. WAINERDI

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* This series of papers is the result of a Conference on *The Status of Multiple Sclerosis* held by the Section of Biology of The New York Academy of Sciences and the National Multiple Sclerosis Society, April 17 and 18, 1953.

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Part I. Biological and Pathological Methods

QUO VADIMUS IN DEMYELINATING DISEASES?

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National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Md.

In presenting the opening paper of this Monograph on the Status of Multiple Sclerosis, I see my function largely as introductory. The papers which follow are by men actively at work in this field. There are an additional number of papers bearing directly on multiple sclerosis which could be given if space permitted, and an even greater number whose relationship to this problem is at present unrealized, but will become apparent in the future. All of these really represent an adequate answer to the question, "Where are we going and what are we doing in the field of multiple sclerosis?"

There have been numerous contributions from clinical neurology which are so often taken for granted that they tend to be overlooked, from the very discovery of multiple sclerosis as a disease entity 115 years ago to its magnificent description by Charcot at the end of the last century. Since that time, clinical neurology has added continuously to our knowledge of the natural history and manifestations of the disease. Its role in the future will be increasingly important to the scientific description of the disease, discovering leads for laboratory research and for objective and critical evaluation of therapy.

The most recent study on the natural history of the disease is the work of Kurland and his collaborators on the epidemiology of this disease. Here we find reduced to incontrovertible facts certain aspects of the distribution of the disease which may stimulate the discovery of its etiology and, at the very least, present a number of interesting features of the disease with which any hypothesis concerning its etiology must be compatible.

Pathology, like clinical neurology, has already made some of its most important contributions, and these contributions, like the alphabet, are both taken for granted and are yet indispensable. The very term "demyelinative disease" is based upon the discovery of its pathological nature; but pathology has done more than describe the morbid process of the disease. In the case of multiple sclerosis, pathology has served to a large extent to explain the clinical features of the disease in terms of location and extent of the lesion. This science is not content to rest upon past glories. Newer specializations and techniques will continue to make contributions in the field. We need more specific staining techniques that are better correlated with cellular biochemistry, a widening of the modalities of observation to include not only visible light but also the utilization of ultraviolet and infrared absorption, electronmicroscopy, and X-ray diffraction, to mention some of the newer techniques which will be applied to an increasing extent to multiple sclerosis.

Then there are the daughter sciences which might be called experimental pathology. Research is continuing in experimental demyelinating disease produced by virus, by allergic response, and by genetic insufficiency. Such research may establish one or another possibility as the actual cause of clinical multiple sclerosis. At the very least, experimental research will provide valuable material for the study of types of demyelinating diseases, their minute course, pathology, and the factors which influence them.

The contributions of physiology such as those that I have already mentioned are now self-evident and tend to be forgotton. It requires more than the mere location of a lesion to explain the clinical manifestations. There must have been a great background of functional localization before a real explanation was at hand. Some of the physiological techniques that have been used in diagnosis are the techniques of electromyography and electroencephalography, and we must not overlook the basic research which led to their development.

What of the role of the circulation? It has already been demonstrated that there is no generalized reduction in the cerebral circulation associated with multiple sclerosis. This fact, however, does not rule out the possibility of localized changes, but techniques for the measurement of the local circulation of areas of the brain in man remain to be developed. Even if an actual reduction in localized nutrition is found to be associated with the sclerotic areas there will still remain the question of the cause of this local change on the basis of thrombosis, vascular spasm, or other mechanisms.

In clinical biochemistry, we find a discipline in the full bloom of youth in its relationship to multiple sclerosis. We have come a long way from the time when the only chemical abnormality was a disturbed colloidal gold curve in the spinal fluid. Challenging evidence is being acquired for a variety of biochemical derangements reflected in the peripheral blood or the cerebrospinal fluid. Characteristic changes in the electrophoresis pattern of these fluids will be described in this monograph. Alterations suggestive of derangements in intermediary carbohydrate metabolism or in phosphorylation have been found in other studies.

All of these findings are exciting and challenging. At the very least, they indicate new diagnostic possibilities but, in addition and more important, they may be a clue to the fundamental biochemical derangement, or even a biochemical etiology of the disease.

But these changes which we are fortunate enough to have found in the blood may be merely a reflection of still more fundamental changes in cellular metabolism. Here we have a science still in its infancy with regard to multiple sclerosis. There is much which we must know: the nature of myelin, which newer physicochemical techniques may elucidate; the mechanism of its formation, probably involving energy-rich phosphorus compounds. It is undoubtedly incorrect to think of myelin as an inert and stable substance. It is probably dynamically involved in continued disintegration and replenishment. Isotopic tracers will shed light on its rate of turnover, and enzyme and lipid chemistry may help to elucidate its formation and normal deterioration. Demyelinative diseases may not be characterized at all by an increasing rate of destruction of myelin and the actual difficulty may be found to lie in some defect in its continued replenishment.

But even these changes may not be primary and, if the etiology should be found to reside in a virus or microorganism, then the biochemist would be studying merely the effects of the disease until biochemistry had advanced to the point at which a biochemical explanation of the infectious process was at hand.

So we complete something of a circle. It is difficult to predict what line of attack will arrive at the primary causes of the disease. All the disciples must therefore be permitted and encouraged to bring their special skills into the field; which brings us to the question of how to direct research into multiple sclerosis.

It is easy to direct research, but only if we know in advance the answers we are trying to find. Then we can judge the value of individual approaches. We may say, for example, that one avenue will lead us to the fundamental etiology, while another will deal only with secondary manifestations. But we never know those answers beforehand, and the individual scientist is usually unaware of the significance of his research before he accomplishes it. It is quite possible that the piece of research that makes the greatest contribution to multiple sclerosis in the next several decades will not even have the words multiple sclerosis in its description.

The National Multiple Sclerosis Society is performing an invaluable function, not by assigning research projects and compelling their accomplishment, but by focussing attention on the problem of multiple sclerosis, by adding new financial support to the total and still inadequate funds for medical research, and by educating the scientists in various disciplines to the importance of this particular problem. For there is no one more interested in making great and beneficial discoveries than the man of science himself.

It is as if we had an army of men shooting at targets through a dense fog. If these men are as highly motivated as I know the average scientist is, it is enough to light up the targets and to give them better guns in order to improve the score.

GENETICALLY CONTROLLED DEMYELINATION IN THE MAMMALIAN CENTRAL NERVOUS SYSTEM*

By Pinckney J. Harman

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Laboratory, Bar Harbor, Me.

Neurological disturbances associated with myelin sheath involvement have been described in many animals other than man.[1] The present study is the outcome of several years of interest in abnormal myelin as found in the central nervous system of rabbits and mice in the genetically controlled colonies maintained at the Jackson Memorial Laboratory at Bar Harbor, Me.

About 20 strains of animals with motor disturbances are present in the stocks at this laboratory and are being preserved by controlled breeding. The genetics of the animals is a primary interest of the resident laboratory staff, but it is often possible to produce them in sufficient numbers so that they become available for other methods of study.

With the cooperation of several scientists at the laboratory, an investigation of the behavior and of the histology of the CNS of several inbred strains has been instituted. These animals include the hereditary ataxia in the rabbit of Sawin, which has been well described by him in collaboration with Anders,[2, 3] and mouse mutants in the colonies of G. D. Snell, M. M. Dickie and E. S. Russell.

The present description pertains in particular to the wabbler-lethal mouse discovered by Dickie.[4] This juvenile lethal is an example of an experimental animal whose production can be controlled, and it is one which may prove to be very useful in the elucidation of the phenomenon of demyelination.

It may be well to call attention here to the fact that attempts to find the physical or histological basis for behavior abnormalities in genetic strains have not always been crowned with success. Perhaps because of previous failures, there persists among pathologists considerable scepticism toward the promise of such efforts, and this attitude has extended to the geneticist. It is part of the purpose of this paper to demonstrate that, in the animal chosen for discussion, a histological basis for the aberrencies in behavior is present and that this alteration in morphology may be controlled genetically. The facts will be reviewed in the following order: (a) clinical signs; (b) genetic background; and (c) histopathology.

(a) *Clinical signs.* Signs of abnormality in the behavior of wabbler-lethal mice are detectable at two weeks of age and, after pursuing a progressive course, are later accompanied by serious derangements in the animals' health, so that it is extremely rare for them to survive six weeks of postnatal life. Death usually ensues between day 21 and day 23. The affliction accordingly runs its course within a single month following onset, a distinct advantage in staging and in testing materials for possible therapeutic value. The abnormal behavior of the mice, including locomotive difficulties with swaying of the body

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* Aided by grants from the Playtex Park Research Institute and the National Institute of Neurological Diseases and Blindness, U.S.P.H.S.

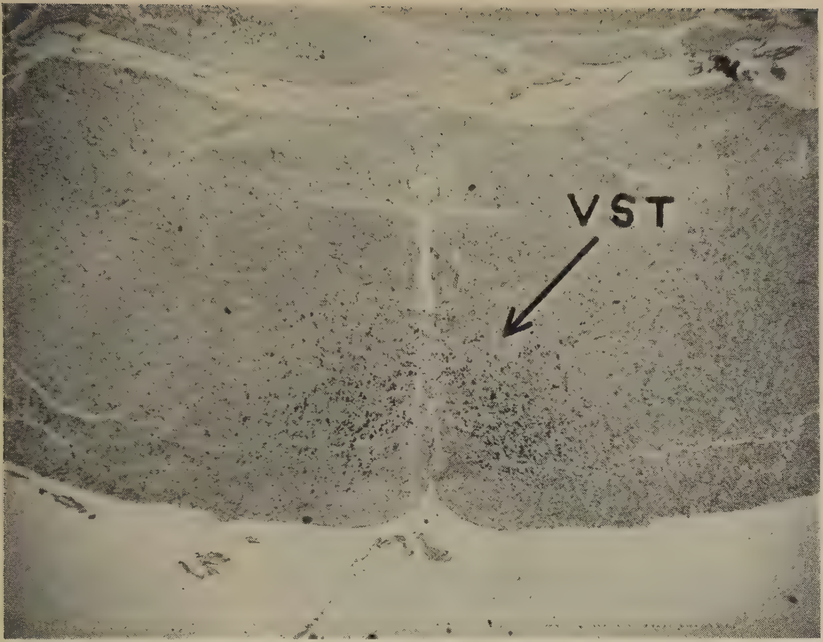

Figure 1. Unretouched low power photomicrograph of a transversal section through the lower medulla oblongata of Wl Wl aged two and a half weeks. The arrow points to Marchi degeneration in the vestibulospinal tract (VST) on the right side of the section.

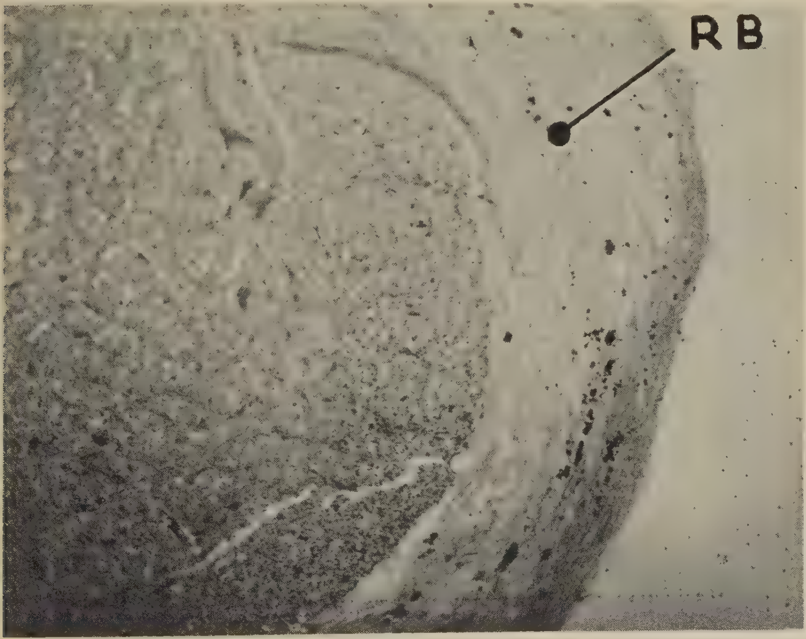

Figure 2. Unretouched photomicrograph of a transversal section through the upper medulla oblongata of Wl Wl aged two and a half weeks. The ball point of the leader is placed among the Marchi clods within the restiform body (RB).

and dragging of the hind limbs and progressive incoordination of the limbs in walking, is easily detected with a little experience.

(b) *Genetic background.* Genetic studies by Dickie have revealed that the disturbance is associated with the mutation of a single gene which is dominant over the normal gene. The heterozygous animals are slightly affected but breed normally, so that the gene may be carried in the heterozygous condition. Three types of animals are produced; the homozygous lethal Wl Wl, the heterozygote Wl wl, and the homozygous nonlethal, or normal, wl wl. These three classes approximate the expected ratio of 1:2:1.

(c) *Histopathology.* While the genetic nature of this disorder was under scrutiny we were particularly concerned with the question of whether the CNS of these animals was implicated. Previous experience has impressed on us the importance of using a method with positive criteria in searching for histological changes. In the present study we have relied a great deal on such a method; namely, that of Marchi. This technique, when properly controlled, displays degenerating myelin with exquisite sensitivity and consists essentially in suppressing the usual reaction of OsO_4 with normal myelin by pretreatment with bichromate; however, it providentially permits the osmication of degenerated myelin to proceed unaltered. The result is the presence of jet-black clods, including ellipsoids, granules, and the like along the course of the disorganized tracts.

Comparison of slides from normal and affected animals has demonstrated that the presumptive homozygous lethal animals all show heavy CNS involve-

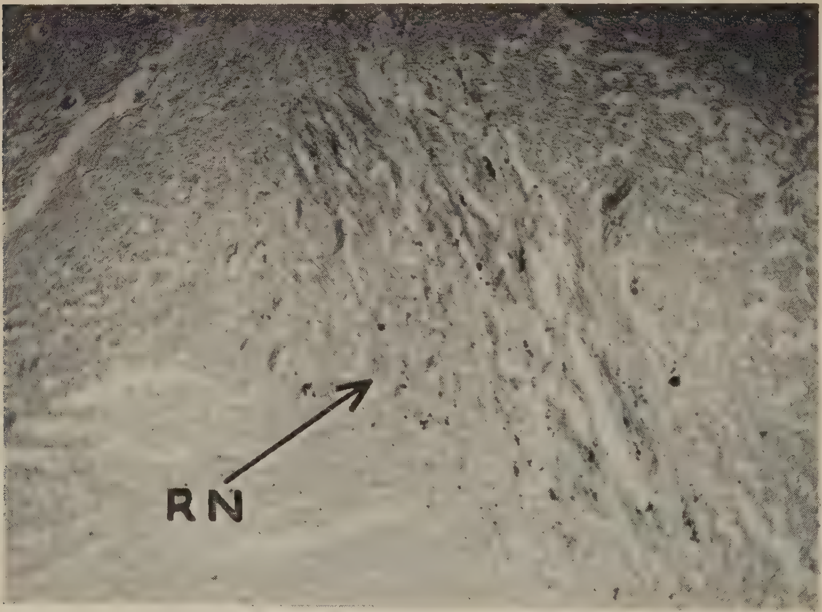

FIGURE 3. Unretouched high power photomicrograph of a transversal section through the midbrain. Arrow points to the accumulation of Marchi degeneration within the red nucleus (RN).

ment. On the other hand, Marchi degeneration is not present to any marked degree in the controls. The heterozygote, which has mild signs of incoordination, may show a moderate amount of degeneration in a single tract (the vestibulospinal), whereas mice with normal behavior are free from such degenerations.

Under such circumstances, we may be permitted to accept the Marchi degeneration so strikingly present in the homozygous lethals as genuine and very likely related to the pathological genetics of the animal.

The heaviest degenerations are confined to parts of the vestibulocerebellar and spinocerebellar systems. Degeneration in the vestibulospinal tract (FIGURE 1) may be traced in serial sections from the lateral vestibular nucleus to the spinal cord. Degeneration is also intense in the entering fibers of the eighth cranial nerve, the juxtarestiform body, the medullary center of the cerebellum, the medial longitudinal fasciculus, the trapezoid body, and the lateral lemniscus. Since these mice have apparently normal hearing and normal auditory reflexes, the possibility suggests itself that the trapezoid and lemniscus fibers represent the pathway of the ascending vestibular tracts whose course is so little understood. The restiform body (FIGURE 2) and both spinocerebellar tracts are heavily involved as is the brachium conjunctivum, the red nucleus (FIGURE 3), the rubrospinal and tectospinal tracts. No degeneration whatsoever was found above the thalamus, whereas all funiculi of the spinal cord were strikingly positive, especially the ventral and lateral columns.

Discussion

The histological findings in wabbler-lethal described above are well correlated with this animal's motor disturbances, since the integrity of the systems showing degeneration is known to be necessary for normal locomotion.

That the myelin sheath in these systems is incriminated is also clear, since degenerated or improperly formed myelin is present throughout the affected systems. We have not, however, settled the cogent questions of whether the abnormal myelin is a true degeneration of previously formed myelin and whether the altered myelin is primary to any other histological change. We have attempted to answer these questions by following the changes from the time of birth. Abnormal myelin is present as are some changes in the cells of origin in the vestibulospinal system at the time of onset of the first signs at two weeks, but is not detectable to any marked extent at birth, when there is little myelin present. Neither are cell changes evident at birth. It seems that the abnormal myelin, the cell changes, and clinical signs first appear at about the same time, and that this time corresponds to the initiation of myelination of the tract in question. Under such conditions, the chronological sequence of changes is difficult to resolve. Since there is no evidence, however, that the cell changes precede those of the sheaths, the possibility of a primary process affecting the myelin sheaths through a failure of some genetic mechanism remains as one alternative in wabbler-lethal. This alternative is rendered the more probable by the fact that changes in the myelin sheaths often have a longer latency than cytological changes.

The usefulness of animals of the type described for research on human disease is of course problematical. There is, perhaps, a closer resemblance here with the familial ataxias of children than with multiple sclerosis. Nevertheless, the fact that demyelination, at least in the sense of abnormal myelin, is present, and that this phenomenon may be produced at will by genetic control, provides the investigator with a new research tool of considerable promise.

Some preliminary attempts to use wabbler-lethal as an assay animal have been initiated. Certainly the efficacy of any material for test could easily be suspected if the life of the affected animals were prolonged. It is hoped that such studies, as well as further investigations on the mechanism of gene action in wabbler-lethal and analogous animals in genetically controlled populations, will ultimately contribute to the clarification of the riddle of the demyelinating process in mammals, including man.

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THE DYNAMICS OF EARLY BRAIN DISEASE WITH PARTICULAR REFERENCE TO MULTIPLE SCLEROSIS

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Multiple sclerosis still offers some baffling problems as to its etiology. There are in the literature and in other papers included in this monograph carefully considered arguments in favor of the most favored theories. It will not be within the province of this discussion to consider them critically or to advance any novel etiological interpretation. The *raison d'etre* of this paper is to point out a common denominator in several of the most favored views. This discussion will deal with the dynamics of early brain disease. The etiological theories of multiple sclerosis which converge at this realm are three. First, is the view that virus invasion is the cause of multiple sclerosis, and that it is a pathological entity most closely related, for example, to herpetic or western equine encephalomyelitis. The second theory is that endogenous antigens from within the nervous system induce, perhaps with the facilitation of unknown factors, an allergic state. The antigen-antibody reactions consequent upon this generation or release of antigens and the hypersensitivity so induced are then thought to lead to inflammation and the destruction of tissue. The third theory related to our subject is that which interprets the disease as a consequence of the more ordinary allergic states which are built around exposure to antigens foreign to the body. It must not be supposed from this statement that the other theories exclude the operation of the dynamic mechanisms which are to be detailed in this paper. It is merely that the other etiological interpretations do not demand this relation. The author is fully aware, also, that there is much overlapping and other relationship of the various theoretical interpretations to the point that some, such as that favoring hereditary mechanisms, are more credible with the acceptance of one or several other theories than as a lone explanation.

The dynamic picture of early brain disease which I am presenting is the outgrowth of a series of studies which has been carried on with Doctor Robert Good, Doctor Fred Kolouch, Doctor William Townsend, and Doctor John Hyde. To these colleagues and students goes grateful acknowledgment. The sequence of researches which will be summarized here revolves around the differentiation of simple from allergic or hyperergic inflammation. It has led into the cytopathology of neurotropic and other virus disease, into the question of the function of the lymphocyte, to an elaboration of the theory of the plasma cell as a source of antibody secretion and, finally, to a study of the mechanisms of acute brain disease.

Initially the investigations grew out of the work of Kolouch (1938), who showed the effects upon the reticulum of the bone marrow produced by the injection of bacterial antigens into rabbits. The plasmacytosis which was regularly induced in this way was correlated with the degree of hypersensitivity achieved. In a second study, in which Doctor Good and I joined Doctor Kolouch (1947), the phenomenon was extended to simple antigenic stimulation and the close relation of the plasma cell to antibody production and allergic processes was confirmed. Prior to, during, and following these studies a series of papers from the Scandinavian laboratories reporting concurrence of plasmocytosis and antibody production appeared, stimulated by the clinical observations of Huebschmann (1913) and of Bing and Plum (1937). These investigators also provided substantiation of the concept which linked the plasma cell to antibody production and hence to allergic processes.

The conspicuousness of the plasma cell in encephalitis in our herpetic rabbits impressed us, as did the published observations of Michels (1931) and of Michels and Globus (1927 and 1929). We thus began a series of observations on the origin and significance of the brain plasma cell and on the interaction of anaphylaxis with virus encephalitis which I wish to present here.

Our starting point of the cellular pathology of simple inflammation has been derived principally from the monograph of Maximow (1929) on the morphology of the mesenchymal reactions. The connective tissue reactions were again investigated by Kolouch (1939), who emphasized the role of the circulating lymphocyte as a source of inflammatory cells. Doctor Townsend and I thought it worthwhile to repeat these observations so that they might serve as a good beginning for our understanding of the inflammatory process. There is an invasion of the connective tissue spaces by neutrophiles and small lymphocytes. From the work of Clark, Wood, and Ebert, we know that the invasive white cells leave the circulation in the smaller vessels and migrate through the vessel walls into the surrounding spaces under the influence of an inflammatory stimulus. The evolution of the lymphocyte toward the macrophage takes place in the first 24 hours. This change is accomplished by the increase in cell size and by the alteration of the nuclear chromatin pattern from one with dense clumping of the chromatin to a pattern of finer and much more scattered nuclear aggregations. A well-marked stage, which we have termed the intermediate polyblast, shows the effects of these changes. In about 24 hours, the lymphocytic cells have become identical with the tissue macrophages and are charac-

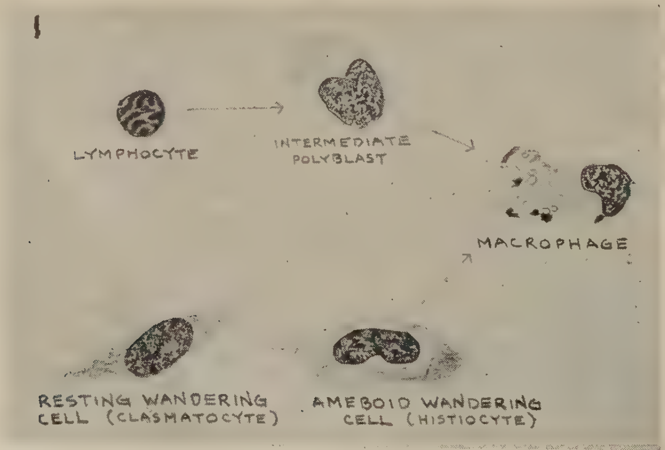
1
LYMPHOCYTE
INTERMEDIATE POLYBLAST
MACROPHAGE
RESTING WANDERING CELL (CLASMATOCYTE)
AMEBOID WANDERING CELL (HISTIOCYTE)

FIGURE 1. The evolution of macrophages in simple inflammation of the subcutaneous tissue. Cells are rendered as they appear in tissue-spreads stained with Wright-Giemsa.

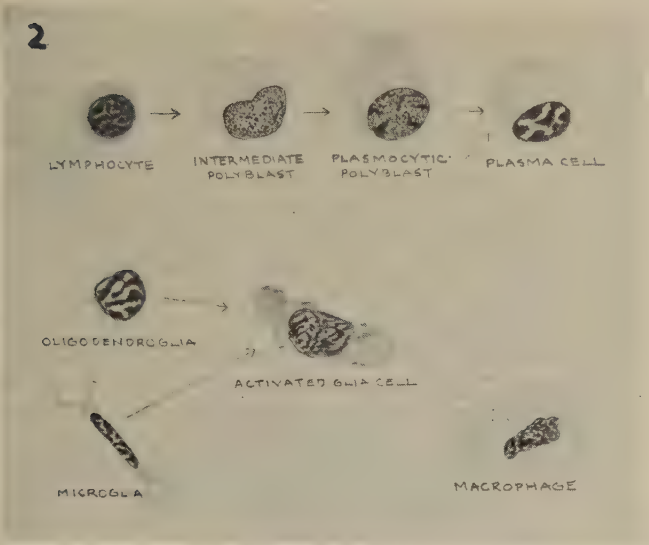

FIGURE 2. The evolution of inflammatory cells in the brain as seen in allergic and simple inflammation. Microglia processes are from sectioned material; all other structures are shown as they appear on the brain imprint stained with Wright-Giemsa.

terized by irregular nuclei and foamy cytoplasm. FIGURE 1 shows the relations in a schematic form. The conspicuous and important early invasion of the neutrophile leucocyte has been left out of this discussion as it has no direct bearing on these phenomena.

In our study of brain inflammation, we utilized similar preparations of inflammatory sites showing the cytology during the early hours of the reaction to foreign materials. As the hematological techniques are far superior to the usual neurological staining methods for the detailed cytology of the inflammatory cells, imprints of the inflamed areas of the brain stained with Wright-Giemsa were used as an adjunct for ordinary histological sections. The simple inflammatory sequence of the brain was found to be similar to that in connective tissue with an evolution of phagocytes from the invasive lymphocytes and from the resident glial cells (FIGURE 2). As we have evidence of the participation of the oligodendroglia as well as of the microglia, we have tended to use the term "mesoglia" for the two types of cells.

These studies served as a starting point for an endeavor to interpret the brain plasma cell. As the reticuloendothelial cells of the body could be induced to enter a plasmacytic cycle by antigen stimulation, the question which was uppermost was "What circumstances give rise to the brain-plasma cells and from what are they derived?" Microinjection of antigens into the cerebral cortex of rabbits has solved this problem. The experiment was set up as follows: a series of rabbits was divided into two groups. Those of the first group were sensitized to egg white and were considered the experimentals. The remainder were left unsensitized. Both groups received microinjections of egg white into the cerebral cortex, about 0.03 cc. being administered with a fine syringe. At short intervals, for four days, the areas were removed and studied by sections and imprints. In the control group, where no previous sensitivity to the egg white had been induced, the ordinary inflammatory cycle described above was noted. A slight amount of lymphocytic infiltration occurred in the neighborhood of the injected material, and some of the adjacent glial cells began to round up and to show increased amounts of cytoplasm. In 48 hours, macrophages from both sources of the inflammatory cells were found. No plasma cells were found until 96 hours and then but few were noted.

In the experimental series, where the animals had previously been sensitized to the egg white, quite another picture was seen. A much longer inflammatory lesion was caused by this same sized injection and the intermediate polyblasts, of lymphocytic and apparently glial origin, were seen to undergo changes to the plasma cell. An extensive population showing these changes was apparent at 72 hours. The experiments were repeated with horse serum as antigen instead of egg white with identical results (Good, 1950).

As a next step, a timed series of rabbits which had been inoculated with herpes simplex virus through corneal scratches were examined for the first appearance of plasma cells. These cells were detected on the fifth day, about the time that, in our experience with this disease, the first rise in temperature may be expected to occur. At five days, when the first plasma cells were detected, the perivascular cuffs were merely incipient, and we must conclude that plasmacytosis affected the earliest wave of invasive lymphocytes. The details of the maturation of these brain-plasma cells have been published (Campbell, 1949, Campbell and Good, 1949), and will not be reviewed here. The conclusion, however, that the neurotropic virus diseases involve allergic responses to some powerful antigenic substance, is the purpose of the mention of that work at this time. The two likely possibilities, as far as the identity of the antigen itself, are (1) that the virus is the primary antigen; or (2) that the destruction of the nerve cells by the parasitism of the virus releases some antigenic fraction of nervous tissue itself. Which of these alternatives obtains in the neurotropic virus diseases is as yet an unanswered question.

That fractions of nervous tissue might serve as adequate antigenic stimulation for the productions of encephalitis has, of course, been demonstrated by the early work of Rivers, Sprunt, and Berry (1933) in the production of brain disease by isoimmunization with brain tissue. This phenomenon, leading to the disease known as "allergic encephalomyelitis," has become a useful and common laboratory entity since the potentiation of this effect by the use of Freund's adjuvants was introduced by Morgan (1946) and by Kabat, Wolf, and Bezer (1946). The opportunity to correlate the cytopathology of a purely allergic brain disease with the findings in neurotropic virus infection was seized, and a series of guinea pigs was prepared by inoculation of homologous brain tissue and an adjuvant mixture of killed *Mycobacterium butyricum* in liquid petrolatum and Falba. A satisfactory percentage of the animals so treated became ill with typical symptoms after a latency of 13 to 22 days.

A detailed analysis of the cytology of the inflammatory cell population of these animals was made. The concurrence of plasmacytic changes in the invasive lymphocytes as well as in the reactive glia was found and has been reported (1950).

Perhaps the most interesting facet of the disease mechanisms uncovered in the study was the analysis of quantitative effects in antigenic stimulation. Compared to the allergic lesions produced by injecting egg white or horse serum into previously sensitized animals, the allergic inflammation of this disease seems overwhelming. There was a much greater participation of the glia than in the experimental lesions. The transformation of the invasive lymphocytes to plasma cells seemed to be hurried and a larger variety of the intermediate polyblasts were seen. In addition to the perivascular cuffs a large number of diffuse lesions were to be seen, particularly along the floor of the fourth ventricle. The inflammatory cells in these spots are predominantly activated glial cells.

At this point, it will be well to consider the neural phenomena described above in terms of the whole animal. In none of the situations which I have described have the brain lesions been understood in their full import without reference to changes in the general reticuloendothelial system of the body. In the simplest experiment, that of injecting foreign protein directly into the cerebral cortex, the animals were prepared by previous sensitization to the antigen and showed the general plasmacytic activation of the reticulum, which Kolouch, Good, and Campbell (1947) showed to be the accompaniment to hypersensitivity. Without the changes in the spleen, lymphoid organs, and bone marrow reticulum, there is no anaphylactic reaction. The role played by these activated reticuloendothelial cells is undoubtedly that of antibody secretion.

We have similarly found that the early incidence of plasmacytic changes in herpetic encephalitis of rabbits is matched by similar changes in the bone marrow and other organs. In other words, we must consider this acute encephalitic infection an acute disease, in the broad sense, even though there is reason to think that the virus is rather strictly limited in its distribution within the body. The obvious integrating system which causes the body as a whole to react with the acute disease syndrome to an infection of the nervous system, is the circulation. From the nature of the cellular reaction of the reticuloendothelial system throughout the body, we may conclude that strongly antigenic substances are carried from the site of the infection to the rest of the body. Whether this is the virus itself, or a product of the tissue suffering primary damage from the virus, can not be answered as yet.

This consideration of the body as a whole is even more illuminating in the instance of the experimental disease called allergic encephalomyelitis. The production of an allergic pathology in the brain, in the wide variety of animals in which the disease has now been produced, depends either upon a lengthy series of systemic injections or a single exposure to a combination of brain antigens in conjunction with exceedingly strong bacterial antigens. In the series which Doctor Good and I reported in 1950, we chose to make a rather thorough examination of the hematopoietic organs as well as of the brain. In the spleens of the diseased animals, we found the tumorous condition that strong antigenic stimulation produces. Cytologically, the lymphocytic series showed a phenomenon which could scarcely have been understood in the material which we had previously examined. Whereas, in hypersensitivity to egg white or horse serum and in neurotropic virus disease the reticulum cells of the hematopoietic organs showed the alterations to what Rohr (1936) has called the plasmacytic reticulum and thence to plasma cells, in these highly stimulated animals the younger members of the lymphocytic, as well as the reticulum cells, were stimulated towards plasmacytic changes, and from them the more compact variety of plasma cells were formed. This is the cell lineage which Moeschlin (1946) has described. In our studies of the spleen of animals suffering from allergic encephalitis, we were able to show the continuity of these apparently divergent mechanisms of plasma cell formation. FIGURE 3 shows an interpretive diagram of this cell lineage.

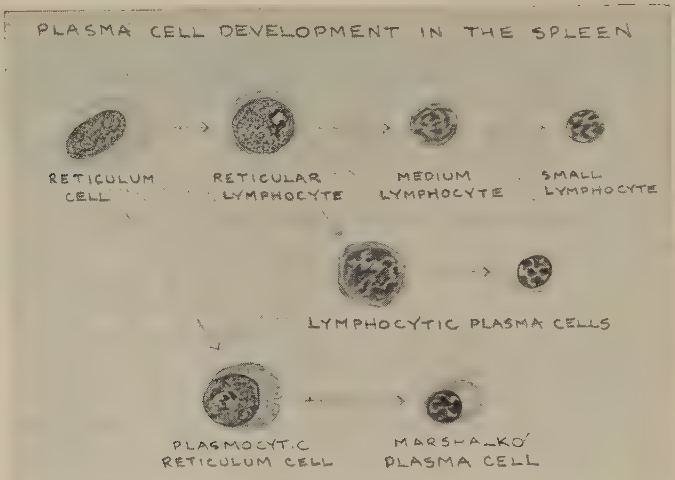

FIGURE 3. The formation of the plasma cell in the spleen as seen in acute allergic encephalitis in guinea pigs. The uppermost line represents the normal lymphocytic derivation from the hematopoietic reticulum. The lowermost line shows the origin of the Marshalko cell from the plasmacytic reticulum of Rohr, itself a derivative of the hematopoietic reticulum cell. The middle line of development, the lymphocytic plasma cell phylum, is shown as offshoots from the reticular lymphocyte. Between the latter cell and the large lymphocytic plasma cell lies the plasma-blast of Moeschlin (not illustrated). All cells are drawn from splenic imprint, stained with Wright-Giemsa.

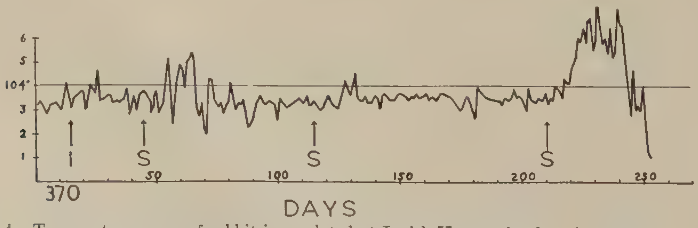

FIGURE 4. Temperature curve of rabbit innoculated at I with Herpes simplex virus and subjected to anaphylactic shock at the three times marked S. The original virus was recovered nine months after the initial injection.

Inasmuch as the neurotropic and allergic encephalitides show a close relation to the generalized bodily reactions, some experiments reported earlier by Doctor Good and myself (1948) are helpful in elucidating the relations between acute and chronic mechanisms in brain diseases. In the large number of inoculations of herpes simplex virus into rabbits, it was noticed that a considerable fraction of the animals showed clear and sometimes severe manifestations of encephalitis but then proceeded to get well. Though residual symptoms such as disposture or head tremor were observed in this series, as a general rule, their reversion to good health was accompanied by a regression of obvious neurological signs. A low incidence of exacerbation of the disease was noted which was calculated at 1 per 200 exposure days. It was found, however, that this rate of exacerbation could be increased fiftyfold by rendering the animals sensitive and then subjecting them to anaphylactic shock. Figure 4 shows the temperature record of an animal (No. 370) which showed a mild but definite disease, following inoculation. In the ensuing seven months, this animal was subjected to three anaphylactic shocks. Following each of these, a typical encephalitis ensued though each was performed in an asymptomatic period. These induced bouts of the disease varied in severity, the first being severe, the second rather mild, the third fatal. After the death of this animal, virus was recovered from its brain tissue and was found to be identical with that which was originally inoculated. Because the induced disease seemed to be an activation of a dormant infection, the phenomenon was spoken of as "precipitation." In all, a series of 19 such precipitations was obtained in 44 animals by subjecting them to anaphylactic shock. Figure 5 illustrates a typical series of these experiments. In these animals, pooled samples of brain tissues were subjected to virus assay by corneal inoculation in other rabbits and titration through mice. The evidence showed that the original disease was again precipitated.

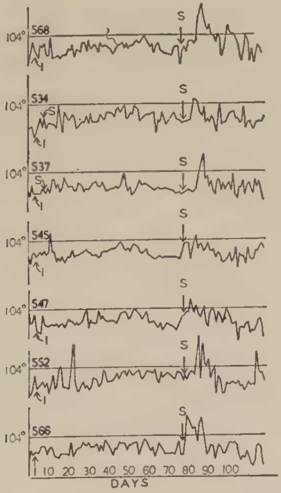

Figure 5. Temperature curves from six rabbits showing precipitation of latent Herpes simplex infection following anaphylactic shock. I = inoculation of virus. S = administration of shock.

This precipitation phenomenon links the course of neurotopic virus infection with the state of the whole organism. However, many questions remain unanswered. We do not know whether it represents a specific effect of anaphylactic shock or the general result of stress. There seems to be no correlation, in this series, with the amount of shock induced. In rabbits, one can grade the shock according to the visible manifestations, which range from complete prostration to inconsequential or no signs. Applying such a grading in these animals failed to reveal a correlation with the severity of the shock. This would seem to argue against nonspecific stress, for animals that did not show any distress at the challenging injection were also susceptible to its precipitating effects upon the infection. It would seem more related to an effect of the challenging dose upon the reticuloendothelial organs themselves.

The seeming double nature of these processes of early brain-disease mechanism deserves some comment. On the one hand, the processes appear to the neuropathologist as localized and sometimes rather restricted lesions. On the other hand, they show dependence upon the body as a whole, as the previous evidence has shown. There are some additional experiments which are *a propos* at this point reported by Hyde and Campbell (1951), which deal with the cytology of the sites of microinjection of virus into the cerebral cortex. Using much the same technique which Good used in order to provoke local allergic inflammation, we injected very small quantities of virus suspension. The virus used were herpes simplex and vaccinia. In each case, control injections were made of the same virus suspension after heat inactivation. The difference between the lesions made by the proliferating virus and that which was inactivated was very great and was of the same nature as in the phenomena seen in the injection of simple antigens. No difference was found in the reaction of these rabbits to the two different viruses. FIGURE 6 shows the rather inconsequential population surrounding the vessels in the immediate neighborhood of one of the control injections, in this case, inactivated vaccinia virus after a lapse of 96 hours. FIGURE 7 shows the cells surrounding a vessel in the immediate vicinity of an injection of live vaccinia virus in calf lymph, also a 96-hour lesion. It can be seen that the bulk of the cells are plasmacytes though macrophages are also to be seen. The contrast between the cells in the experimental and control series is also to be seen in imprint preparations of the same sort of experiments. FIGURE 8 shows the cells of the control lesion. These are typical phagocytes. FIGURE 9 shows the plasmacytic population in the experimental lesions. Both of the foregoing are 96-hour preparations. A comparison of the experimental and control lesions at 48 and 96 hours may be made from TABLE 1, which is a summary of the cell populations. These experiments indicate that proliferating viruses act as very strong antigens. They provoke reactions analogous to simple antigens in animals which had been previously sensitized. In the experiments in question, previous exposure to these viruses was out of the question. We may conclude from this basis that, under these circumstances, viruses exhibit antigenic properties of a rather special nature, and also that they are able to provoke, as local responses, the same early pathological sequences that the more generalized virus infections show.

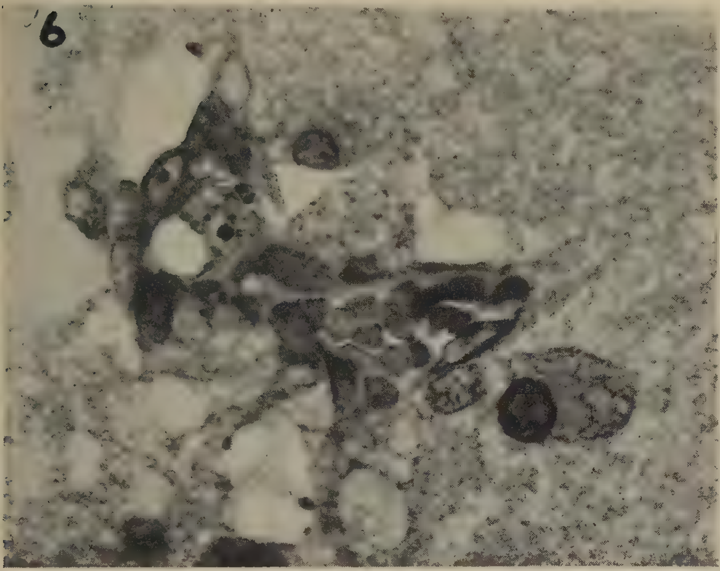

Figure 6. Section of blood vessel in the immediate proximity of a 96-hour lesion produced by injection of heat-killed vaccinia virus into the brain of a rabbit. Cresyl violet and erythrosin stain.

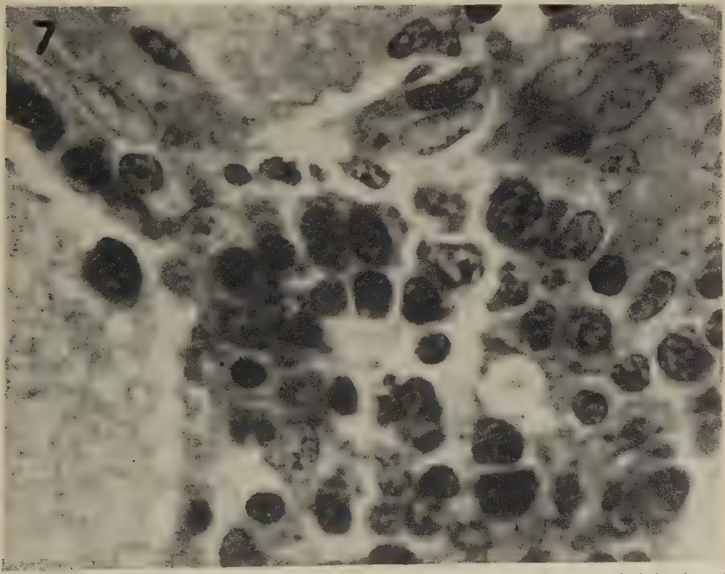

Figure 7. Tangential section of perivascular cuff from region of 96 hour lesion made injection of infective vaccinia virus into rabbit brain. Cresyl violet and erythrosin stain.

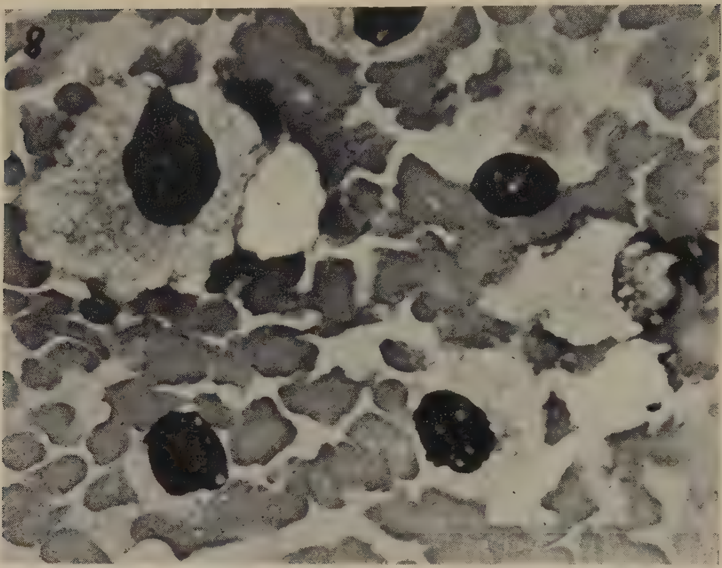

FIGURE 8. Representative cells from an imprint of 96-hour lesion resulting from infection of heat-killed vaccinia virus into the brain. Wright-Giemsa stain.

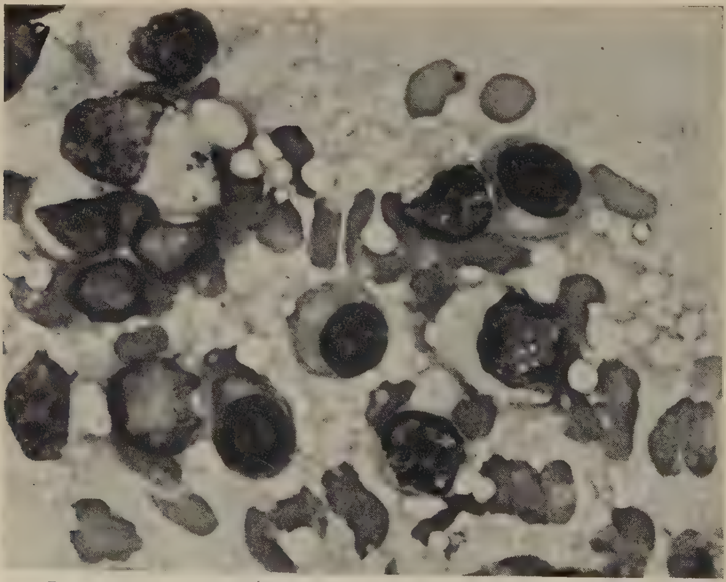

FIGURE 9. Representative cells from an imprint of 96-hour lesion resulting from infection of infective vaccinia virus into rabbit brain. Wright-Giemsa stain.

TABLE 1

INFLAMMATORY REACTION OF RABBIT BRAIN TO VACCINIA VIRUS

Time		Infective virus	Heat-killed virus
48 hr.	Perivascular cuff:	+	0
	Intermediate polyblasts:	++	++
	Plasmacytic polyblasts:	+++	±
	Macrophages:	+	++
	Plasma cells:	+	0
96 hr.	Perivascular cuff:	+++	0
	Intermediate polyblasts:	++	++
	Plasmacytic polyblasts:	+++	+
	Macrophages:	+	++++
	Plasma cells:	++++	+

The inflammatory mechanism which is analyzed by these experiments, as was mentioned in the introduction, is consistent with several of the most convincing models of multiple sclerosis. As the common denominator of this disease and of all of the experimental lesions which we have shown is the cytological reaction to antigenic stimulation, there is little in this work to pinpoint the particular etiology of the human disease. Causes and origins of the malady will probably have to be established by the more specific methods of serology and by epidemiology. Inspection of this data, however, does offer some aid in the formulation of an operation *anschauung* in the field of multiple sclerosis. Though a serious gap in our information exists concerning the evolution of local acute inflammatory lesions to chronic demyelinations and plaques, the meaning of what has been presented here is that the early mechanisms offer the best insight into the diseased condition. It is also clear that the brain is not an isolated organ in regard to these pathological states, but that the disease should be related to the body as a whole. In particular, the reticuloendothelial organs and the serum should be included in any discussion of the encephalidides, acute or chronic.

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Discussion of the Paper

Doctor Byron H. Waksman *Neurology Service, Massachusetts General Hospital, Boston, Mass.:* I feel that much of the histologic material which Doctor Campbell has presented us as established fact remains in the realm of speculative hypothesis. Many of the cells which he calls plasma cells would be identified by other histologists as lymphocytes or small macrophages. The supposed evolutionary sequences from oligodendroglia or microglia through intermediate stages to plasma cells are based on the study of material stained by the routine hematologic methods, which are not capable of distinguishing oligodendroglia from other cells with nuclei of similar size and shape. Doctor Campbell has indicated that he has not used the usual silver methods in identifying these cells. He has further suggested that many cells can develop from type A to type B or C and vice versa with equal ease, a possibility not supported by any other work of which I am aware. It is recognized by most workers in this field that the evolutionary sequence in a series of cells can not be easily determined by observing these cells together in a stained section or smear, the only method employed in the present work. The suggested correlation of Doctor Campbell's findings with those of the Scandinavian workers and others, who have established a relation of plasma cells to antibody formation, is accompanied by a postulated cellular evolution completely unlike that accepted by the workers in question. I should like to remark also that I cannot understand how Doctor Campbell can attribute the type of sequence he observes to sensitivity when he finds the identical sequence of reactions, qualitatively, quantitatively, and in time, in nonsensitive animals injected with living virus.

Doctor Campbell: One must distinguish between speculation, interpretation, and fact. The experiments by which these facts are established have been described here and in previous papers. The interpretations are in accordance with the experience and viewpoint of the observers. Because the microscopic methods used in neuropathological laboratories are inadequate for the study of cytodynamics, and because inflammation is best approached from the hematological point of view, standard microscopic methods have been used, sections supplemented with imprints. The analysis of cell lineage in experimental inflammation depends upon a critical use of timed series. Though this approach is long overdue in brain histology, it is commonplace in the rest of experimental anatomy.

The matter of the early response of the body to virus antigens is a particularly interesting one. The evidence is clear that such a rapid plasmacytosis can be elicited by these agents, not only in the brain but, as shown the experiments of Bjerneboe and Gormsen, also in the connective tissues. Four days is probably not too short a time for the establishment of an allergic response, but it is evident that the bacterial and, particularly, the virus antigens are especially powerful in this respect. This factor may well be a correlate of their pathogenicity.

RETURN OF SPINAL CORD FUNCTION IN MAMMALS AFTER TRANSECTING LESIONS

By L. W. Freeman
Indiana University Medical Center, Indianapolis, Ind.

It appears no longer necessary to speak of the possibility of regeneration of the spinal cord. In our laboratories[1, 2] as well as in others,[3, 4] there have been ample demonstrations that regeneration can and does occur. This statement is little more than a confirmation of the experiments reported by Cajal almost 50 years ago. In FIGURE 1, taken from the spinal cord of a rat who walked after the spinal cord had been transected, one can see quite clearly the growing end bulbs. Attention is drawn to the similarity of this illustration to the drawings made by Ramon y Cajal.[5] If, then, regeneration does occur, why has it not been found with greater regularity? It is the purpose of my discussion to point up some of the known factors which prevent the demonstration of regeneration. Again, one turns to Cajal and finds that he, in contrast with the usual interpretation of his findings (probably because of translation difficulties), outlined many of the factors which prevented the demonstration of regeneration.

One need only recall that, until rather recent time, the prognosis for a patient with a spinal cord injury was relatively hopeless. Indeed, it was commonly quoted in many textbooks that the life expectancy of a patient with a complete spinal cord transection was 18 months. Analysis of the cause of death of these patients generally shows that the major complications which led to death were urinary tract difficulties and decubitus ulcers. With the advent of improved bladder care as introduced by Munro,[6] complications in the urinary tract were reduced. With the outbreak of the World War II and with the accumulation in military centers of large numbers of paraplegic patients, methods for care of these patients become standardized to some extent. Also, the advent of antibiotics and the widespread use of blood transfusions added considerably to the abilities of the physicians to prolong the lives of these patients. The use of rehabilitation techniques complemented the other factors to the point where today it can be stated with certainty that "every patient with paraplegia who is intelligent and cooperative can be brought to a measure of medical, physical, and social rehabilitation compatible with a normal life expectancy."[7] I have previously referred to this statement as the "Munro Doctrine." Turn then to the situation in the animal. The care of a paraplegic animal is one of the most difficult tasks that one could undertake in experimental medicine and surgery. The mortality in such animals is tremendous. The personnel required to maintain these animals in good health far exceeds that of almost any other circumstance in the laboratory. Cajal, admitting to inability to cope with the multiplicity of difficulties in transected animals, turned to incomplete lesions in order to get his histological pictures. In this day and age such lesions are eyed with suspicion. Consequently complete transecting lesions are necessary and one must simply devise a means whereby the complications can be avoided.

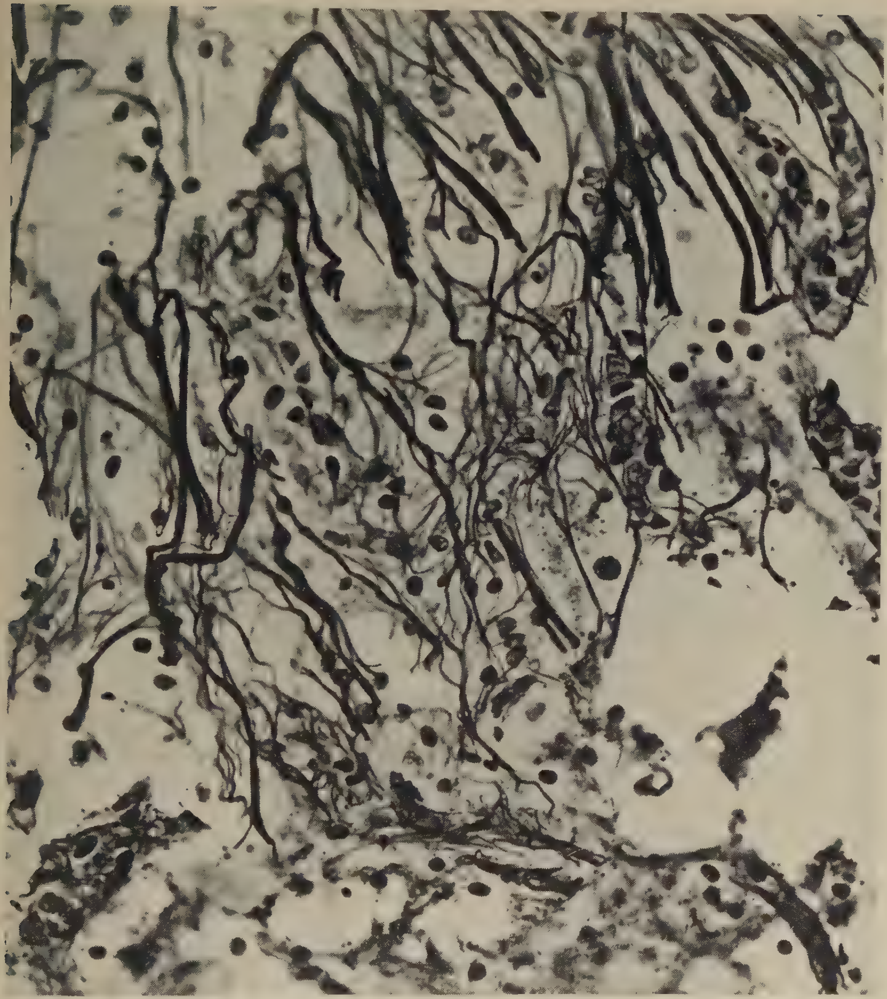

FIGURE 1. Longitudinal section of the spinal cord of a rat which walked some months after a transecting lesion; silver stain.

The urinary tract is the primary source of early death, after operative and anesthetic mortality. In FIGURE 2, one sees the typical pyelonephritis, with the course continuing from here to perinephric abscess, rupture, and death. Such infective processes are common throughout the entire urinary tract. If the animals survive this early period of infection, they are prone to the development of urinary tract calculi as seen in FIGURE 3. One accordingly sees in the experimental animal much the same course of events that is shown by the relatively neglected human patient. The same possibilities for the development of decubitus ulcers and gangrene are augmented in the experimental animal by

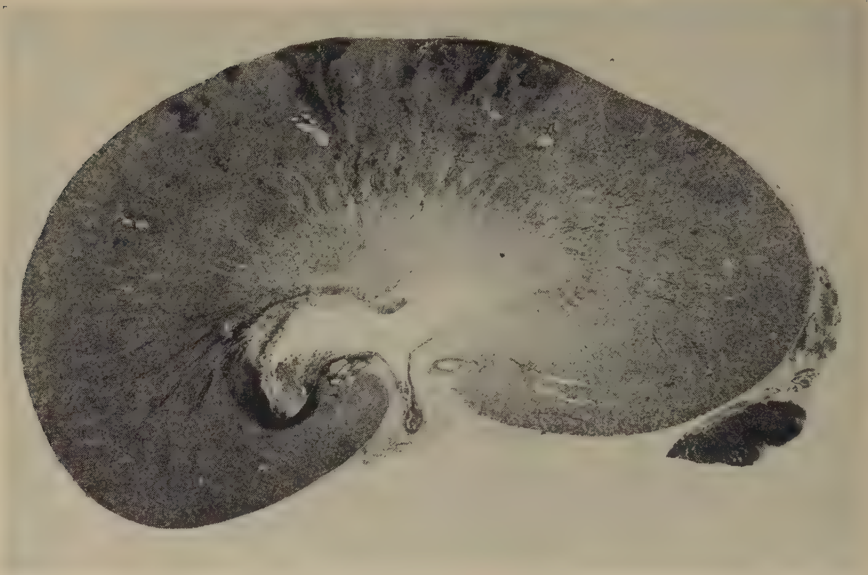

FIGURE 2. Cross section of kidney of a rat which died several weeks after transection of the spinal cord, stained with hematoxylin and eosin. Note the pyelitis and pyelonephritis.

self-cannibalism. Just as the human patient shows a great increase in protein catabolism (so much so that the average loss of weight for paraplegic patients during the last war was approximately 50 lb.), so too does the experimental animal demonstrate this same phenomenon. The albumen-globulin ratio in the serum is reversed. The hemoglobin falls precipitously. There is marked intolerance to adrenalin. There appears to be a major change in adrenal cortical function. Gathered together, all of these phenomena spell death for the animal unless they can be counteracted completely.

When one examines the factors that play a role in regeneration of any tissue, one of the principle features appears to be that of an anabolic state. Certainly the factors that I have outlined so far have no resemblance to anabolism but rather the reverse—catabolism. Indeed, the paraplegic patients that were seen early in the past great conflict were so depleted that they did not even show regeneration of such vigorously capable tissues as epithelium and liver. Certainly, the central nervous system does not equal the capabilities of other tissues in regenerative capacities. It is accordingly hardly logical to assume that, in the catabolic state wherein vigorously capable tissues do not show their qualities of regeneration, weaker structures would do so. The problem, therefore, rests around restoring the entire organism to a state of anabolism, so that the central nervous system can express its regenerative qualities. It should be clear from these comments that it would be highly unlikely that patients treated in the present fashion, for the most part, would show regeneration in the spinal cord. It could be predicted that, when all of the advances of modern medicine are applied to such patients, a certain number will definitely show regeneration.

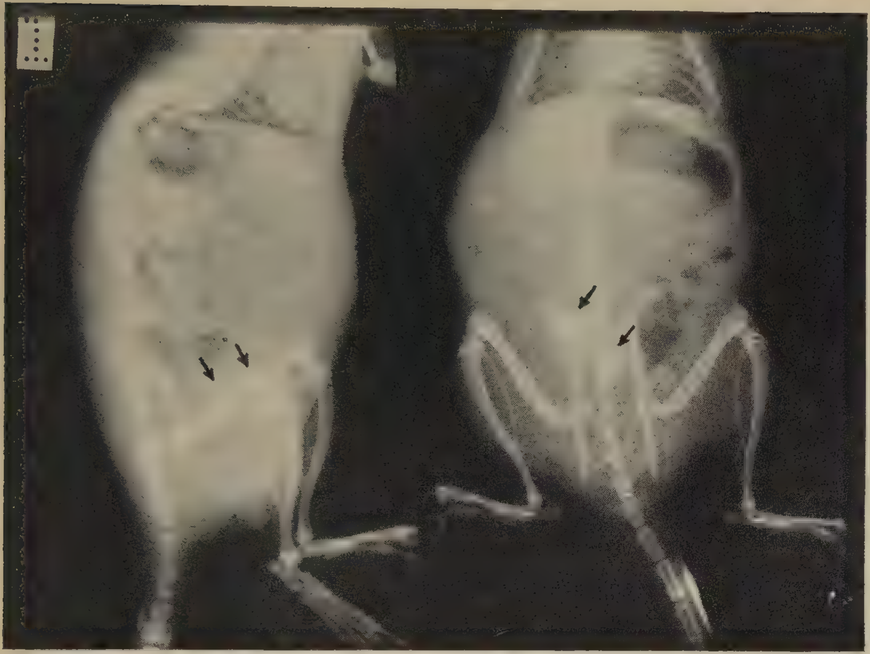

FIGURE 3. Anteroposterior and lateral roentgenograms of a rat which failed to show evidences of return of function for some months after the spinal cord had been transected; two calculi in the urinary bladder are indicated by the arrows.

After the factors just outlined come the events that occur at the site of injury to the spinal cord. There are certain general concepts which I should like to discuss with you. First, lesions to the human spinal cord are generally violently produced and are of an extensive nature. Even a presumably minor injury can result in extensive hematomyelia which can destroy the cord for

TABLE 1

COMPARISON OF RATS WITH SPINAL CORD TRANSECTIONS AFTER INTRAPERITONEAL INJECTIONS OF A NONPROTEIN BACTERIAL PYROGEN WITH OTHERS (CONTROLS) RECEIVING PLACEBO INJECTIONS

Discarded animals represent those which failed to survive long enough for functional evaluation to be made. Note the improved status after the administration of one gamma per day for 30 days.

	No.	Discards	No. used	Useful function		Nonuseful function		No function	Average duration of life
				Good	Fair	Poor	Slight		
Controls	88	22	66	6	9	12	25	14	136 d.
Pyrogen 1 gamma/d. for 30 d.	36	3	33	10	6	1	15	1	216 d.
Pyrogen 1.5 gamma/d. for 45 d.	25	11	14	—	—	7	6	1	118 d.
Pyrogen 3.0 gamma/d. for 45 d.	13	3	10	—	2	1	7	—	112 d.

long distances. Second, the surgical concepts of such injuries have not kept pace with the approach in other organs of the body. I refer to the fact that surgical debridement used in compounded injuries, burns, and general missile injuries is not usually carried to the spinal cord. Indeed, the débridement concepts have just recently been accepted for the brain. Usually the spinal canal and the spinal cord itself have been allowed to harbor foreign tissues. The same statement holds true for fracture-dislocation injuries that are not treated by clearing the spinal canal. Gathered together, these factors spell disaster to a normal healing procss. As such, the lesions are not exclusively problems of repair in the central nervous system. It is clear from the work of Windle that the glial barrier is one of the important factors. The glial barrier itself, however, is only one of the many referred to. In those transecting lesions which are produced surgically in a clean fashion, when there is a broad fibroblastic scar intervening, few if any fibers penetrate to the opposite stump. If this fibroblastic scar be augmented by obvious physical barriers such as intervertebral disc material, bone, or other foreign elements, then one can understand quite readily why regeneration is not commonly seen. Thus the problem centers around providing the best possible milieu for regeneration to express itself in its best sense. It is around these factors that our present researches are directed. We have presently been working in our laboratories with a preparation which, upon subarachnoid injection at the site of the surgical lesion, appears to do a miraculous job of preventing fibroblastic scarring. We have found that, at a given dosage, an agent which prevents the formation of a glial barrier has given functional benefit (TABLE 1).

We thus return to the original question of why regeneration does not generally occur in the spinal cord. Since we have shown functional regeneration in the rat, cat, and dog after transecting lesions of the spinal cord, it is clearly no longer a question of why doesn't regeneration occur, but what stops it from expressing itself functionally.

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Discussion of the Paper

DOCTOR WILLIAM F. WINDLE (*Travenol Laboratories, Morton Grove, Ill.*): I am pleased to note that Doctor Freeman reports favorably on the use of the drug Piromen in his spinal rats. I am not surprised that doses greater than 1 gamma per rat failed to benefit. In current studies on spinal cats and monkeys, we are using a febrile dose of 0.5 to 1.0 gamma/kg. of body weight, which is only about one tenth of the dose his group has used.

I should like to take this opportunity to point to certain differences between our results and those of Doctor Freeman's group, and to seek comments on them. In the first place, we cannot support the view that any significant regeneration of intraspinal neurons occurs in the usual course of events after transecting the spinal cord. In all of the spinal cats in our studies over the last few years, we have found that transection is followed by glial and connective tissue scar formation between the cut ends of the cord, even when the ends of the cord are closely approximated. Only on extremely rare occasions at points where the glial scar is scanty have we ever seen nerve fibers pass out of the stump of the cord and become lost in the scar. It is our opinion that intraspinal regeneration does not take place unless the formation of a pia-glial membrane is inhibited in some way.

The main contribution that our group has made to the subject of regeneration of neurons in the central nervous system is the demonstration of a means of inhibiting the formation of this pia-glial scar barrier. This end has been accomplished by means of the drug Piromen, a pyrogenic bacterial polysaccharide derived from a *Pseudomonas* species. This drug is not necessarily the only agent by which such inhibition can be effected. A certain amount of inhibition followed the administration of ACTH although this appeared to be much less than that obtained with Piromen. Also desoxycorticosterone was able to inhibit the formation of this barrier, but cortisone failed to do so.

In view of the differences between our experiments and those of Doctor Freeman's group, I wonder whether or not he has always been dealing with complete transections of the spinal cord. Is Doctor Freeman producing a single complete transection, or is he performing two hemisections close to one other, as seemed to be implied in the paper given at a recent meeting in Columbus, Ohio? It has been our experience that nearly normal walking will take place in a cat in which no more than five per cent of the ventral funiculus neurons of each side has been left intact in a transecting lesion of the spinal cord.

Another question I have regarding Doctor Freeman's work relates to the ages of the animals which he uses in his studies. He has made it fairly clear, I believe, that some of his operations were performed on puppies and kittens. Were his operations on rats likewise carried out in young individuals? Does he in the usual course of events think that regeneration of intraspinal neurons is more likely to occur, without any drug therapy, in young mammals than in adult mammals?

DERMAL AND SEROLOGICAL REACTIONS TO NERVOUS TISSUE ANTIGENS IN MULTIPLE SCLEROSIS

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Skin reactions exhibiting the gross and histologic characteristics of the delayed or tuberculin type have been observed in animals with experimental allergic encephalomyelitis tested with homologous white matter.[12] The character and distribution of the lesions in the experimental disease are similar to the pathologic findings in certain of the human demyelinating diseases, in particular in acute disseminated encephalomyelitis.[1]

The present investigation was undertaken to determine whether a similar reactivity to nervous tissue could be demonstrated in patients having demyelinating disease. Accordingly, skin tests and serologic studies with normal human white matter as the test material were performed on patients with multiple sclerosis.

Experimental Methods

Patients. Thirty-eight ambulatory and bed patients, in whom the diagnosis of multiple sclerosis had been established beyond reasonable doubt, were tested. Eight of these were male and 30 female. The age range was 10 to 60, average 33. In the 26 patients having a chronic form of the disease the neurological findings were indicative of multiple lesions in the central nervous system and, by history, it was determined that the disease had occurred intermittently. Twelve patients were tested either during an exacerbation, when symptoms and signs were still at their peak, or within a few weeks of the occurrence of such an exacerbation. Four patients were tested during what appeared to be a first attack of multiple sclerosis, a diagnosis that was supported by the subsequent remission of the symptoms. Four patients having acute disseminated encephalomyelitis associated with measles were tested five to eight months after the subsidence of the acute phase. Forty control patients, chosen at random on the neuromedical and neurosurgical wards, were also tested. Of these control patients, 19 were male and 21 female. The age range was 18 to 76, average 49.

Skin tests. The patients with demyelinating disease and the controls were tested intradermally on the flexor surface of either forearm with one or more of the following materials.

(1) Five samples of human white matter from the frontal lobes of patients dying of carcinoma, cardiovascular disease, or liver disease were employed. Each sample was ground in a Potter-Elvehjem mill to give a 10 per cent suspension in physiologic saline and then autoclaved. Autoclaving does not affect the capacity of white matter to produce experimental allergic encephalomyelitis in animals[6] or to elicit the skin reactions seen in that disease.[11] One tenth ml. of one of the five preparations was employed for each intradermal test.

(2) Semple rabies vaccine (Lederle #2078-92), consisting of a 20 per cent

suspension of rabbit brain and containing phenol as a preservative was used in 0.1 ml. amounts. It was selected as a test material because it is a commercially available, standardized preparation of heterologous nervous tissue, and because it is known occasionally to cause acute disseminated encephalomyelitis in man.

(3) Brucella abortus febrile antigen (Lederle, Parke Davis) was washed several times and resuspended in sterile physiologic saline containing 0.5 per cent phenol. The final suspension contained 0.022 mgm. N per ml. This vaccine, being an irritative particulate antigen, was chosen as an additional control, and a test dose of 0.05 ml. was used.

(4) Old tuberculin (Massachusetts State Laboratories) was used in a concentration of 1:10,000 (test dose 0.1 ml.). Tuberculin was employed inasmuch as it is a well-known standardized test for a specific reactivity of the delayed type.

Reactions were observed at 20 minutes, 24 hours, 48 hours, and after a period of one to four weeks. Each reaction was evaluated at each time on the basis of induration, erythema, edema, and necrosis. In certain instances tests were repeated after an interval of a few weeks.

Serological studies. Sera were obtained from all patients at the time of the initial tests and about three weeks later, and were stored at −15° C. They were inactivated at 56° C. for 20 minutes immediately before use in the conventional complement fixation test.[7] Dilutions between 1 and 160 were set up with antigen and with six 50 per cent hemolytic units of complement, and incubated for 45 minutes at 37° C. before the addition of sensitized sheep red cells. The antigen was normal human white matter, finely ground as a 0.05 per cent suspension. Veronal buffer containing optimal amounts of Ca^{++} and Mg^{++} was used throughout. Tests carried out under these conditions are entirely satisfactory for the demonstration of circulating antibody in animals injected with nervous tissue.[7]

Results and Discussion

The results of the intradermal tests, recorded as diameters of the wheal or papule and of the erythema are tabulated in TABLE 1. The size and other characteristics of the reactions were not correlated with the activity of the disease process. The reactions of the multiple sclerosis patients differed from those of the controls only by a greater erythema at 20 minutes and 24 hours in response to white matter, and at 24 and 48 hours in response to rabies vaccine.* No immunologic significance can be attributed to this difference, which may result from an increased vascular reactivity in multiple sclerosis.[4, 9] Repeat tests with white matter, some subjects being tested as many as five times with different white matter samples, did not in general elicit any increase in reactivity.

In almost all subjects the injection of antigenic material was associated with the immediate appearance of a wheal and flare. The two nervous tissue preparations gave rise to larger immediate reactions than the Brucella or the tuberculin, possibly on the basis of undetermined irritant properties. At 24

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* These differences were significant at the 2 per cent level when tested by χ^2.

TABLE 1

SKIN REACTIONS IN DEMYELINATING DISEASE*

Test material	Subjects	Readings (diameter in mm.)																			
		20 minutes					24 hours					48 hours					Late				
		No. of tests	Wheal		Erythema		No. of tests	Papule		Erythema		No. of tests	Papule		Erythema		No. of tests	Papule		Erythema	
			Median	Range	Median	Range		Median	Range	Median	Range		Median	Range	Median	Range		Median	Range	Median	Range
White matter	MS	42	12	5–15	40	20–57.5	42	5	0–25	15	0–32.5	40	5	0–11	6	0–21	37	4.5	0–8.5	5	0–11.5
	Controls	43	12	4–40	40	0–70	45	5	2–15	6	0–17.5	37	4	1–25	4	0–25	32	5	0–15	5	0–15
	Retested Controls	20	12	8–15	30	0–70	20	5	1–10	5	0–10	20	4	1–6	4	0–9	18	5	0–10	5	0–10
Rabies vaccine	MS	40	9.5	2–18	22.5	0–60	40	4	2–20	12	0–20	38	5	0–8.5	7	0–13.5	35	3	0–10	6.5	0–12
	Controls	29	10	3–19	25	0–62.5	29	4	1–10	5	0–15	26	4	1–8	4	0–12	13	5	2–11	5	2–12
Brucella vaccine	MS	38	6	1–11	10	0–27.5	38	5	0–35	13	3–38.5	37	10	0–45	16	0–50	35	5.5	0–10	6	0–22.5
Old tuberculin	MS	38	5	0–10	6.5	0–29	38	0	0–15	0	0–18.5	37	0	0–17.5	0	0–37.5	35	0	0–2	0	0–10
							18†	3	1–15	4.5	1–18.5	13†	5	3–17.5	6	2–37.5					

* 4 patients with acute disseminated encephalomelitis are included in the multiple sclerosis group.
†Figures given for the patients showing definite redness or induration.

hours, the reactions to these preparations consisted essentially of an indurated red papule, occasionally still surrounded by a flare. At 48 hours, the papule was essentially unchanged or slightly smaller. The late observations indicated that in 14 of 69 tests using human white matter and in 10 of 48 tests using rabies vaccine (equally distributed between multiple sclerosis and control groups) a definite reactivation occurred at one to three weeks. Half of these reactions showed necrosis and some were associated with tenderness and itching. In six control patients where two antigens had been used simultaneously, four showed a late reaction to both antigens while two reacted only to one.

A few unusual reactions were observed. One of the five samples of white matter gave larger reactions than the others at 24 and 48 hours, perhaps as a result of an unknown primary toxicity. True urticarial responses, with itching and pseudopod formation, occurred in two MS patients tested with human white matter and in two controls. The tests using rabies vaccine produced this type of response once in each group. Two additional controls and one additional multiple sclerosis patient reacted in the same manner when retested with a different white matter sample. Still another control developed generalized itching and edema on the first test.

One cannot consider any of the reactions of the multiple-sclerosis patients to white matter positive without also considering the reactions of the controls positive. Comparable reactions are seen in nonsensitive individuals tested with other particulate antigens.[5] The late reactions observed are thought to be due to sensitization by the test antigen, since most of them first began to develop more than a week after the tests had become essentially negative. The same applies to the few urticarial reactions seen on repeat testing.

The four patients exhibiting residual neurological abnormalities from a recognized attack of acute disseminated encephalomyelitis did not show any unusual reactions. No conclusions can be drawn inasmuch as too few patients were tested, and these patients were not tested during the acute phase of the illness.

Our data cast no light on the controversy regarding the possible etiologic relationship of brucellosis to multiple sclerosis,[3, 2, 10] since tests with Brucella vaccine were not performed in the control series. Under our test conditions, 48-hour papules greater than 10 mm. were seen in about half the patients. The more marked reactions to the Brucella vaccine did not occur in the same patients who showed large reactions to human or rabbit nervous tissue, and were not correlated with the activity of the disease process.

Only two of the sera studied showed complement-fixing antibody against normal human white matter. Both were obtained from patients with chronic multiple sclerosis, one a patient having had no known recent exacerbation and the other recovering from a recent episode. In the latter, the positive serum was obtained three weeks after the skin tests, the earlier serum having been negative.

Sachs and Steiner have reported complement-fixing antibody in multiple sclerosis when nervous tissue from a case of multiple sclerosis was used as antigen.[8] Since similarity of demyelinating disease to experimental allergic encephalomyelitis was the basis of the present work, any human white matter should have been entirely satisfactory as antigen.

Summary and Conclusions

(1) Thirty-eight patients having MS and four patients having acute disseminated encephalomyelitis were skin tested with one or more samples of autoclaved normal human white matter, rabies vaccine (rabbit brain), Brucella abortus vaccine, and old tuberculin 1:10,000. Forty-three controls afflicted with various medical and neurological diseases were tested with the same nervous tissue antigens. Twenty repeat tests with normal human white matter were performed on control patients several weeks later, some patients receiving as many as five successive tests.

(2) No difference was observed between the reactions of the patients having multiple sclerosis or acute disseminated encephalomyelitis and those of the controls. In about one out of five subjects a reaction to nervous tissue, appearing more than one week following the test, suggested sensitization by the test. No neurological symptoms accompanied this apparent sensitization.

(3) Sera taken at the time of the skin testing and several weeks later were free of complement-fixing antibody against normal human white matter except for two specimens. The one was obtained from a patient having chronic multiple sclerosis who had had no known recent attack; the other was the second specimen from a patient with chronic multiple sclerosis who was recovering from a recent exacerbation.

(4) Skin sensitivity comparable to that seen in animals having experimental allergic encephalomyelitis was not apparent in the patients tested.

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ELECTROMYOGRAPHIC PATTERNS IN MULTIPLE SCLEROSIS

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This discussion is a preliminary study in which an attempt has been made to ascertain what the bioelectrical potentials could offer in the evaluation of patients afflicted by multiple sclerosis. The exact distribution of the pathological lesions in this disease is very difficult to determine. A plaque can evidence itself by some symptoms and reflex changes while plaques can be present elsewhere and not show any subjective or objective signs. At other times, a fresh plaque can develop and would be overlooked because it might be located in an area where some other lesions have already resulted, for example, in transverse damages at different levels of the long tracts of the spinal cord. A plaque can damage any level of the central nervous system but would seldom result in symptoms limited to one long tract. Several symptoms can be attributed to one plaque. There may be a predominant symptom as, for instance, spasticity or ataxia, but usually there is a complex clinical picture reflecting a lesion involving several systems. Still more often there may be multiple lesions. The difficulty of the localization of the lesions is obviously multiplied by the numerous plaques.

Sensory impairments, both subjective and objective, are usually very difficult to evaluate. Pathological reflexes are the most reliable clinical signs of the disease. They constitute objective data. Many reflexes and also motor impairment can be analyzed when electrical potentials are recorded.

Electromyography is the study of the electrical voltage generated by the muscles. Electroneurography can also be studied in man under special conditions. When properly recorded and analyzed, the electrogram becomes a useful agent to the neurological evaluation.

Normal relaxed muscles are neutral, electrically speaking; no voltage is generated. The normal neuromuscular function can be analyzed when a voluntary contraction takes place or when a reflex is elicited. The muscle potentials show activities of groups of muscle fibers and, in suitable conditions, motor units can be studied. A normal motor unit has a given pattern, a certain voltage, duration, and frequency of discharge which will depend on the muscle explored. The ideal investigation would be a study of the behavior of a single motor unit activity but, so far, this has been rather a difficult clinical problem. The isolation of single units is not always possible in the different groups of muscles and, therefore, cannot be used as a basic study for a patient having multiple sclerosis.

Motor disfunction in this disease is frequently characterized by paresis, and often, because of the frequent involvement of the corticospinal tracts, by spasticity. In some of the paretic muscles, bursts of spike potentials of low amplitude and high frequency are often recorded. In some other muscles that appear to be equally paretic or weak, much larger potentials of higher voltage, even greater than those found in the normal, but of smaller frequency, were observed. A study was made in order to find out whether some of those patterns correspond to an incomplete lesion or a to partial demyelination, and whether they would possibly represent reversible phenomena. The reduction in strength of a muscle in multiple sclerosis is usually the result of a lesion of the corticospinal tract, but there are certainly other conditions that can also result in paresis.

Some cases having multiple sclerosis showed marked atrophy. The type of atrophy found can resemble those seen in lower motor neurone impairments and has been said to be the result of those lesions. From my experience, this condition is very rare. A plaque found in the anterior horn cell region usually does not affect the cells themselves and rarely can it affect either part of an anterior or posterior root.

Denervation can be easily shown by the recording of action potentials. The spontaneous activity of muscle fibers resulting from denervation is very characteristic, and is evidenced by sharp monophasic or diphasic rhythmic waves. The negative spike is of one or two milliseconds duration and has an amplitude of 10 to 100 microvolts. Occasionally, smaller or higher voltage can be found. The waves discharge at a frequency of 1 to 15 per second. They often would appear with insertion of the needle electrode into the muscle. At other times, denervated muscle fibers are characterized by repetitive discharges of waves of longer duration: 5 to 15 milliseconds. The waves appear only with the insertion of the recording needle electrode. They can frequently vary between 5 and 10 per second, and can persist for several seconds, sometimes even as long as several minutes. They are positive or negative monophasic potentials. Some of their characteristics have been already described by Jasper and Ballem.[1] I have frequently seen them in peripheral nerve injuries and in anterior horn lesions. They seem to represent rhythmic contraction resulting from the simultaneous stimulation of many denervated muscle fibers, activated by the insertion of the needle electrode. Further, the electrical stimulation of such denervated muscles would show other typical characteristics, which are: slow response to prolonged stimulation; strength-duration curve shifted to the longer time; and prolonged chronaxy figures. If completely denervated, a muscle fails to respond to stimulation of the corresponding motor nerve.

In the many multiple-sclerosis cases that have been tested, such findings were seldom seen. In only two cases were fibrillatory action potentials of denervation found in some muscles of the thenar group, most likely indicating that a part of the corresponding anterior root might have been affected. Denervation resulting from lower motor neurone lesions and eventually from destruction of the anterior horn cells would correspond to irreversible damage and consequently no remission could be expected in the case of such lesions. The electrical studies showed that atrophy, in most cases, was the result of disuse and corticospinal tract lesions, and was not attributable to lower motor neurone impairments.

In some rare cases, a plaque having a sudden onset can result in a clinical picture of a transverse myelitis. Transverse myelitis is usually characterized by complete paralysis below the site of the lesion. The lesions are seldom confined to a narrow area, as several segments are involved. In most of those cases, the inflammatory lesions are diffuse and would often affect most of the distal part of the spinal cord. The upper level being sharply defined, it is therefore called a transverse myelitis but should rather be called a disseminated myelitis with a level. The differential diagnosis between a diffuse myelitis with a level and a transverse lesion caused by a plaque is usually easily made with electrical studies. With the clinical history one can often make the diagnosis of an acute attack of multiple sclerosis with a transverse lesion but sometimes it is a difficult clinical problem. In a myelitis, the electrogram would show evidence of diffuse lower motor neurone lesions which, as stated above, is seldom encountered in multiple sclerosis and, when seen, affects a few bundles of muscle fibers only. A diffuse myelitis extends many segments below the lesion and is characterized by spontaneous fibrillations of denervation. Stimulation of those muscles would easily confirm the diagnosis of diffuse anterior horn cell lesions. The differential diagnosis, obviously, is important. In multiple sclerosis, the lesions may still be reversible, while in diffuse myelitis, they are practically never reversible.

Electromyographic recording facilitates study of the stretch reflexes. In normal conditions of rest, as stated above, the tone is not evidenced by any electrical activity. When a normally innervated muscle is passively stretched, there will be some active resistance to stretch, which is called stretch or myotatic reflex. This stretch results in typical bursts of activity in the electrogram. The very fast stretch of a muscle resulting from tapping on a tendon when a deep reflex is elicited has also a definite electrical pattern in the normal muscle. If muscle tone is increased, though there is no visible activity at rest, the response to stretch can be increased since usually the threshhold is low. This reaction can also be evidenced by an increased response to tapping of the tendon. A muscle can sometimes give the impression of having an increase of tone on routine clinical examination. EMG can easily demonstrate hypertonus or hyperactivity. This activity would be an objective sign that can be recorded and eventually be compared at different intervals. At times, it may be difficult to know whether change in tone is the result of damage to the corticospinal, rubrospinal, vestibular, extrapyramidal, cerebellar, or reticulospinal tracts. The possibilities of lesions affecting different tracts require careful analysis, and the electrogram may possibly help to establish such differentiation.

Reflex activity of the tendon jerks can be recorded by using either surface or needle electrodes but usually it is better analyzed when using the latter. In upper motor neurone lesions the deep reflex has a greater amplitude and is of longer duration. That pathological reflex may be characterized by a tonic component which follows the rapid jerk, and there may also be a spreading of the reflexes. Clinical observation of those reflexes is not always easy, and it is not always possible to compare them from day to day. The recording of the electromyograms and study of their patterns allows more accurate follow-up of the clinical condition. All those phenomena, such as prolonged stretch reflex to passive motion and brisk response of the muscle by tapping of the tendon or eventually the clonus, can be thus recorded and analyzed.

As early as 1904, Sherrington[2] had shown that after deafferentation of a limb in an animal, changes take place in the spinal reflexes. If a crossed reflex is elicited, it becomes exaggerated. In 1928, Bremer[3] had also shown that if a limb is deafferented there is a hyperexcitability of the corresponding spinal cord. This result was demonstrated by an exaggeration of the response to vestibular stimulation. The slightest motion of the head would result in a strong motor discharge of the spinal neurones.

In 1935[4] and in 1936,[5] I studied the regulation of some reflexes of the spinal cord, and reported that in the deafferented animal spinal neurones react differently when tested shortly after deafferentation and when analyzed later in the so-called chronic stage. The difference is marked.

In some cases of multiple sclerosis, the findings are much the same. A plaque can affect the spinal cord in such a way that it may result in an actual deafferentation of a limb or it may sometimes cause a complete or incomplete Brown-Sequard syndrome. After such an acute manifestation, the patient usually has an almost completely paralyzed limb; sometimes both legs are affected. Shortly after, there is a return of function with some spasticity or hypermetria or discoordination. This condition is similar to that found in the experimental animal in which, shortly after deafferentation of a limb, there is a loss of tone and the limb is paretic as if the motor pathway were affected. The leg is dragged when the animal walks; the animal is unable to run. This stage of paresis lasts several days. When the crossed spinal reflexes are studied during that stage and the myograms are recorded, the latent period of the reflex is prolonged. The reflex is sluggish and the recruitment is slowly progressive. The after-discharge is smaller than in the normal. Shortly after deafferentation, there is a stage of pseudoparalysis and depressed reflexes. Soon after the stage of weakness, there is a stage of hypermetria. The motions are brisk and poor coordination is present. The electrogram shows action potentials of high amplitude with greater firing frequency of the motor cells. The induced contralateral reflex in the experimental animal is very brisk, exaggerated, and followed by a prolonged after-discharge. The pseudoparalysis seen in the early stage is very similar to that seen in some patients afflicted with multiple sclerosis in whom a sudden lesion in the dorsal column results in partial deafferentation. This pseudoparalysis has also been described in cases in the preataxic stage of tabes characterized by rapid evolution. Those cases are not frequently seen now owing to antiluetic treatment.

It is not too unusual to see an actual spinal shock in an acute development of a plaque. The reflexes are greatly modified and depressed and, later on, the patient will improve, and slowly some of the reflex responses will become exaggerated. This condition resembles the central hyperactivity resulting from the late effect of deafferentation and indicates a very marked change in the excitability of the central nervous system, a change not entirely attributable to corticospinal tracts lesions.

The response of the deafferented spinal neurones to corticospinal impulses has been recently studied by Stavraky and Drake[6] and by Teasdall and Stavraky.[7, 8] In multiple sclerosis, the reactions to voluntary motions are sometimes accompanied by markedly increased bursts of action potentials and by minimal voluntary contractions, so that one wonders whether there is any similarity with those studies done in the experimental animal. Studies of the electrogram pattern can help us to understand better the physiopathology of the lesions within the central nervous system in multiple sclerosis.

The study of electrically induced spinal reflexes also seems to be promising. Those apparently simple reflexes, some of them monosynaptic, can be analyzed in various pathological conditions. Their study will help us understand not only the excitability of a given cord segment, but may also help to analyze the other different funsions: facilitation, summation, and inhibition. Some of these reflexes, induced by the stimulation of a mixed nerve, have already been studied by Hoffman.[9] The electrical pattern developed by the stimulation of a mixed nerve can result in a reflex which can be recorded and analyzed. Such a reflex, being a functional unit of the central nervous system, if properly analyzed, may give invaluable information. Some of these electrically induced reflexes seem to be similar to the short stretch reflex or tendon jerks. Some may have a more complex pattern. When an electrical stimulus is applied to the nerve the impulse travels both ways. If the common peroneal or tibial nerve is stimulated, there is a contraction of the muscle, which is a neuromuscular response. There is also an afferent impulse going to the spinal cord and resulting in a reflex contraction of the same muscle. The latency of the response for the neuromuscular contraction is very short. The reflex response has obviously a longer latent period. Usually, the threshhold stimulus for the reflex is lower in such a way that if a stimulus is applied to the common peroneal nerve, for instance, it would result in a small contraction after a delay of about 30 milliseconds and the response would take place in the tibialis anterior or extensor communis or peroneus longus muscles. By increasing the strength of the stimulus, the reflex increases, but a neuromuscular response would also take place. Since the latent period of the latter is shorter, it would appear in the electrogram before the reflex response. The neuromuscular response takes place 3 to 4 milliseconds after stimulation, depending on the distance between the part of the nerve stimulated and the location of the recording needles. An example of this reflex is shown in FIGURE 1. When the stimulus is increased, the neuromuscular response becomes more pronounced and the reflex response can be extinguished completely by the antidromic stimulation of the spinal cord. In two patients having multiple sclerosis the study of those reflexes has shown a latency which is greater than in the normal, and greater than in patients that had a corticospinal lesion caused by a cerebral vascular accident. Whether this delay is the result of demyelination is a possibility, and whether those findings represent reversible disturbance in the paresis that accompany that delayed response is also possible. In each of two patients in whom these reflexes were recorded as having a certain delay, there was marked improvement in the function of an affected lower extermity.

In a disease which is essentially polymorphic, where plaques of demyelination can be numerous or few, large or small, and located practically anywhere, the patterns of the electrogram are sometimes unpredictable.

One of the objectives of this study has been to try to find out whether or not

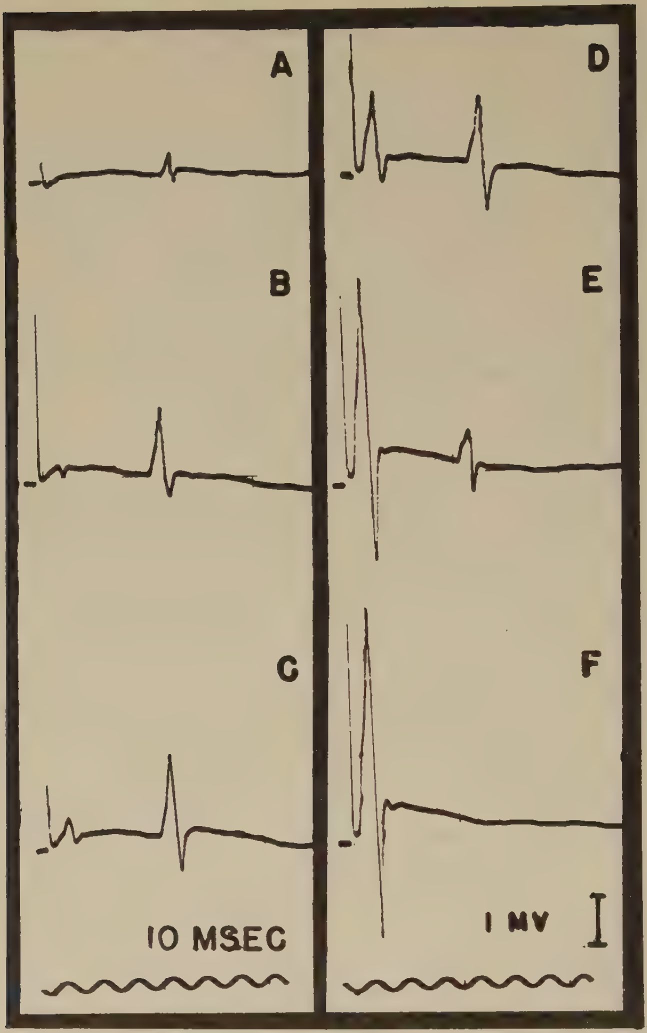

FIGURE 1. Common peroneal nerve stimulation. Duration of stimulus 1 millisecond. Recording of neuromuscular response and reflex contraction from peroneus longus muscle. (A) Reflex response: 32 milliseconds after stimulus artifact. (B) By increasing the strength of the stimulus, the reflex response increases but a neuromuscular response appears 4 milliseconds after stimulus artifact. (C and D) Further increase of stimulus. (E) With greater stimulation, the neuromuscular response increases still more; the reflex response is smaller. (F) With supramaximal stimulus the reflex response is extinguished.

some changes in the bioelectrical potentials would possibly represent lesions susceptible of remission. By no means can the study of the action potentials replace the clinical examination. In some cases, the clinical signs are very few and there may be many lesions, some might be demonstrated by careful electrographic recording.

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CIRCULATORY DISTURBANCES AND MANAGEMENT OF MULTIPLE SCLEROSIS

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Multiple sclerosis was considered by its first describers as something of a curiosity. Advancement in knowledge of the disease and progressive refinements in diagnosis have brought this malady recognition today as one of the commonest among neurologic disorders.

Credit for the first complete clinical and pathologic account of multiple sclerosis is attributable to Charcot, the eminent French neurologist. Charcot first became familiar with the progress of the disease through daily observation of his housemaid, who had nystagmus, intentional tremor, and scanning speech. Ironically enough, Charcot also was a "pioneer" in misinterpreting the condition, for he diagnosed the case as tabes dorsalis.

By means of freehand sections stained with primitive methods, he recognized the essential histopathologic features of the disease and emphasized the loss of myelin sheaths, the preservation of nerve fibers, and the proliferation of glia.

Throughout the 80 years which have elapsed since Charcot's original description of multiple sclerosis, little has been added to the histopathology of the disease. This deficiency has been largely attributable to the apparent futility of repeated descriptions of the nature of the sclerotic palques. These lesions are to be considered as the late sequelae of the disease charaterized by the final process of glial scar formation.

It might be just as futile to attempt to determine, in the case of a small area of the skin healed with scar formation, whether the lesion was initiated by injury, by infection, or by some other pathologic condition. There is indeed nothing specific or pathognomic in any process of scarring.

The chief aim of my own work has been to determine the nature of the *earliest* stage of the pathologic process, and thus to obtain some information concerning the mechanism of plaque formation prior to scar formation. For this purpose, grossly visible sclerotic plaques in the stage of scarring were eliminated. Serial sections were prepared only from grossly intact regions of the brain and spinal cord with the object of tracing the pathologic process from its beginning. The histologic analysis was therefore limited to small microscopic lesions diffusely scattered throughout the central nervous system which were not visible to the naked eye (FIGURES 1, 2, 3, 4).

About two thirds of all the initial small lesions were found in close proximity to small veins which were extremely distended and displayed signs of stasis and congestion. Only some of the veins were occluded by small thrombi composed of fibrin threads and large masses of agglutinated platelets.

Similar observations have been made by Putnam,[1] Dow and Berglund.[2] Putnam and his co-workers[3] were the first to assign a primary role to vascular lesions in the pathogenesis of multiple sclerosis. They succeeded in producing patches of demyelination by intravenous injection of various substances, *e.g.*,

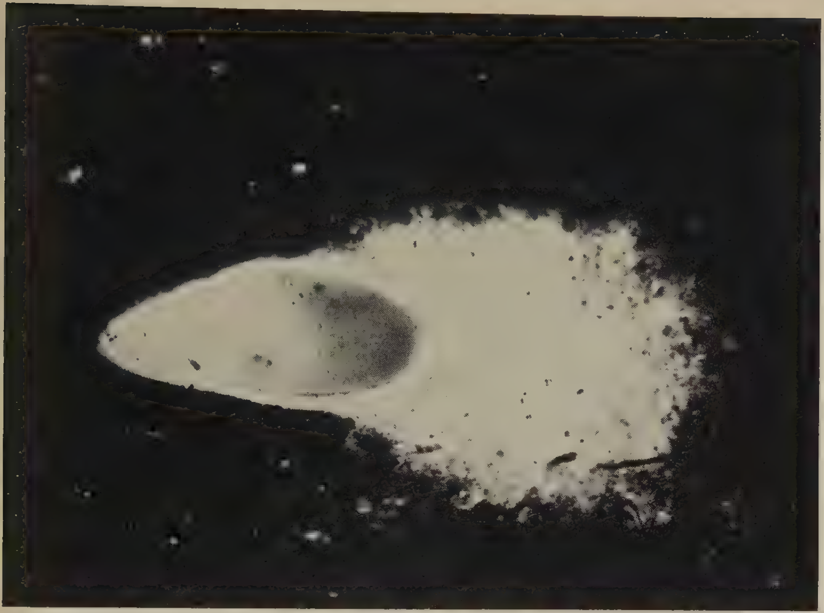

FIGURE 1. Small area of myelin loss in the vicinity of a distended and congested small blood vessel displaying the characteristic signs of vasoparalysis. Spielmeyer myelin sheath stain.

tetanus toxin. The similarity between such experimentally produced lesions and those observed in the early stage of multiple sclerosis would seem to indicate that the early lesions of multiple sclerosis might be also produced by local circulatory disturbances.

Clinical Observations

A clinical study of 250 cases of multiple sclerosis yielded findings that are formulated herewith according to the case by case observations.

Careful questioning of patients concerning their earliest complaints disclosed the presence of a striking increased fatigability of the skeletal muscles in 152 cases (60.8 per cent).

This marked fatigability is confined either to a certain group of muscles involving the one or both upper and lower extremities or, as is more frequently the case, it is of a general nature described by the patient as general "exhaustion" and complete depletion of strength.

The feeling of fatigue or exhaustion, though often induced by a mild physical effort (such as a short walk), also is frequently noted in the circumstances of complete physical rest. The impairment of muscle power, when induced by physical effort, may improve or disappear following a short period of rest.

Actual paralysis of one or several limbs is not usually present in the early stage of the disease.

In numerous instances, patients feel relatively free from fatigue during the early morning and are accordingly capable of performing routine duties daily for the first few hours after awakening. Many of these patients, however,

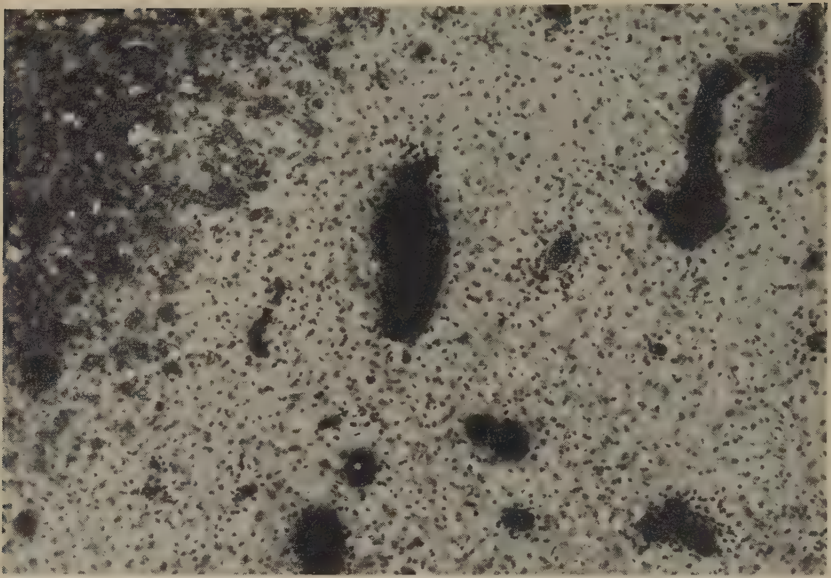

FIGURE 2. Numerous congested and distended capillaries within a small area of demyelinization. Note the sludging of the blood. Spielmeyer myelin sheath stain.

complain that they are "played out" by noon, when they succumb in greater or lesser degree of generalized fatigue.

There are those patients, also, who complain of fatigue from the moment of awakening. "I am as tired in the morning as when I went to bed" is a common report.

It is worthwhile to mention that most of such relatively early symptoms as transient diplopia, paresthesias (in the form of "numbness" or "tingling" in

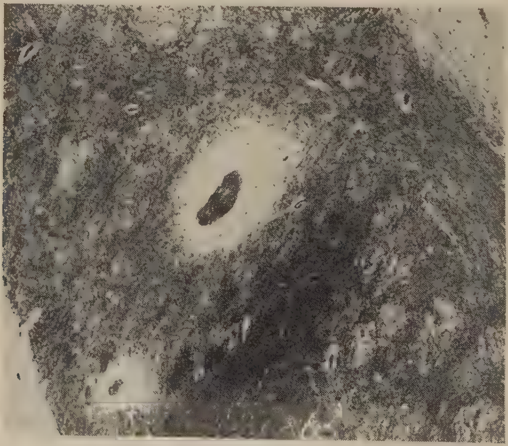

FIGURE 3. Two small congested blood vessels displaying signs of vasoparalysis surrounded by small foci of myelin loss. Spielmeyer myelin sheath stain.

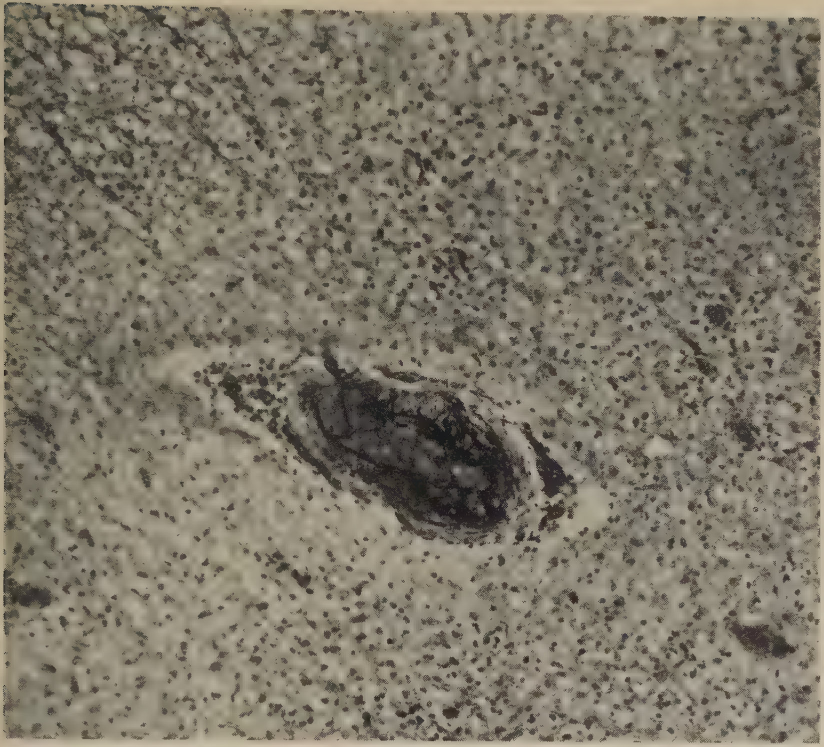

FIGURE 4. Small blood vessel with signs of vasoparalysis occluded by a recent thrombus and surrounded by a small area of demyelinization. Hematoxylin eosin stain.

the extremities), "staggering" gait, awkward use of fingers, occasional difficulty in articulation, and transient impairment of sphincter control are initially manifest coincident with extreme fatigue, and, after a brief interim of rest, these symptoms often subside.

The rapid changeability of symptoms and signs, another characteristic of the early stage of multiple sclerosis, lends itself to misinterpretation. Regarded as "functional" in nature, such a rapid shifting of symptoms and signs from one type to another leads erroneously to their classification as disorders of psychoneurotic or hysterical origin.

Obviously, because the neurologic examination during the early stage of the disease often fails to reveal any definite signs of an organic lesion, misinterpretation of the initial complaints is, unfortunately, all too easy.

Blood Pressure. Blood pressure levels have been accorded too little attention in past studies of multiple sclerosis.

Repeated measurements yielded systolic and diastolic pressures far below normal values in a large number of the present series of cases. In 42 patients (16.8 per cent), in the age group between 21 and 47, the systolic pressure varied between 85 and 98. A systolic pressure between 100 and 110 was displayed at various times in 70 other cases (28 per cent). Finally, a group of 22 cases

(8.8 per cent) reported having had a history of very low blood pressure during various periods preceding the present illness.

In summary, the study of blood pressure revealed a total of 134 patients (53.6 per cent) showing evidence of low blood pressure at various times coincident with repeated examinations.

An attempt at evaluation of these observations in their relationship to the clinical manifestations and to the pathogenesis of the disease is, obviously, complex.

In the author's opinion, the clinical demonstration of low blood-pressure levels in a large number of multiple-sclerosis patients is in harmony with the following clinical and histopathologic observations:

(a) The predominance of symptoms and signs indicative of increased fatigability in the early stages of the disease.

(b) The precipitate onset or exacerbation of the disease by acute infections or by injuries, both conditions being frequently associated with lowering of arterial blood pressure.

(c) Frequent association of the early lesions of the central nervous system with vascular disturbances characteristic of vasoparalysis (Scheinker).[7]

(d) Abnormally low cerebral blood flow in cases of multiple sclerosis (Tucker, Donald, and Farmer).[29]

(e) Repeated demonstrations of venous thrombosis within some multiple sclerosis lesions (Putman and Alexander,[4] Dow and Berglund,[2] Marburg,[5] Scheinker,[6, 7] Fog[8]).

In a recent publication Roizin, Abell, and Winn[9] studied the blood circulation of the conjunctival vessels in 24 patients afflicted with multiple sclerosis. Using a techinque described by Knisely they observed the behavior of blood cells and their flow through the small blood vessels of the conjunctiva. In the first series of 19 patients, 13 showed the presence of sludge (agglutination of blood cells) to a significant degree. In the second series of 18 patients sludge was observed in *all* instances. The authors express the opinion that lumps of sludge may plug capillaries supplying nervous tissue and thus seriously interfere with its blood supply in cases of multiple sclerosis. Needless to say, the process of sludging of blood as described by Roizin is an essential part of vasoparalysis and vasothrombosis and is closely correlated with early lesions of multiple sclerosis as described in the author's earlier publications (Scheinker).[6, 7] Supported by all these observations, the following theory concerning the pathogenesis of multiple sclerosis is suggested:

Multiple sclerosis lesions develop as the result of recurrent episodes of focal disturbance of nutrition by vasoparalytic reactions of the small veins and capillaries of the central nervous system. The vasoparalysis may be preceded by repeated brief periods of vasospasm, as observed by Franklin and Brickner,[10] Grain and Jahsman,[11] Alexander, and others.[12]

In 1947, Franklin and Brickner[10] reported 18 cases of multiple sclerosis in which brief constrictions of retinal arterioles were actually seen during an ophthalmoscopic examination. In three cases, alternate opening and closing of an arteriole were noted.

The vasoparalytic vascular distention as the end-result of short lasting angiospastic phenomena is always associated with stasis and retardation of blood flow. The vasoparalysis of small blood vessels may also be induced by such various etiologic factors as infection, trauma, emotional shock, or similar conditions.

Prolonged and repeated occurrences of vasoparalytic vascular phenomena may result in prolonged stasis and "sludging" of blood. This effect, in turn, may produce thrombotic occlusion of the small blood vessels and thus, through permanent impairment of the blood supply, give rise to circumscribed patches of demyelination.

Proposed as a theory for subsequent reconsideration, this interpretation of the pathophysiologic mechanism affecting multiple sclerosis lesions would, or does, explain the detrimental influence of infectious diseases, trauma, emotional distress, and similar related conditions which, with consistent frequency, precede or usher in the initial clinical manifestation of multiple sclerosis.

Furthermore, the same vascular mechanism may be the most acceptable explanation for the transient nature of some of the clinical symptoms, as it may well also be the most acceptable explanation of the remissions and exacerbations which characterize the disease.

The list of exogenous factors responsible for vasoparalytic reaction of the cerebral blood vessels (acute infection and trauma) tallies in close correspondence with the list of exogenous factors which often precipitate onset or exacerbation of multiple sclerosis.

Therapeutic Considerations

Present day approaches to multiple-sclerosis therapy may be subdivided into three categories:

(1) There is, of course, a contingent of physicians who (regrettably, enough) maintain a nihilistic outlook, presenting to each patient (however discreetly) an unhopeful prospect as a victim of a progressively crippling disease. Specious as it is, their reasoning follows the line that, as long as the cause of the disease remains unknown, any attempt at treatment must be doomed to failure.

(2) Entrenched in empiricism, another group of physicians experiments in the use of various and sundry therapeutic measures irrespectful of their nature, frankly confessing meanwhile to a "shot-in-the-dark" attitude toward attempts at treatment.

(3) In the third category, there are those physicians who, aiming towards the prevention of further development of lesions, focus attention upon the pathogenesis of the disease.

For a detailed discussion of accumulative experience pertaining to several treatment methods, past and present, the reader is referred to the material surveyed in publications by Brickner,[13] Putnam,[14] and Schumacher.[15]

All clinical observations, as were noted in the first part of this paper, were given consideration in the formulation of a procedure for treatment of multiple sclerosis. Therapeutic measures advocated by the writer would, obviously, compose a synchronology complementing statements made, *a priori*, in introduction to this subject.

The proposed management of multiple sclerosis is founded upon the writer's theory of the pathogenesis of the disease. These treatments are aimed at elevation of blood pressure and stimulation of the general blood circulation as a counteraction to vasoparalytic vascular phenomena leading to stasis, sludging, and eventual thrombosis of the small blood vessels.

Specifically in use are daily administrations of a series of vasopressor drugs such as paredrin hydrobromide (60 mgm. or more orally in divided doses throughout the day), desoxyn hydrochloride (in daily oral doses of 5 to 10 mgm.), and small amounts of ephedrin sulfate.

The primary effects of these drugs are measured by repeated blood-pressure readings, and their prescription is adjusted in alternation or in rotation according to the individual patient's blood pressure level.

A marked majority of cases so treated responded with moderate elevation of blood pressure.

Therapeutic measures given second place are those aimed at alleviations of the focal nutritional disturbances produced by alterations in the vasomotricity of the small blood vessels of the central nrevous system.

All patients were given 10 cc. of a 10 to 20 per cent solution of Neo-Calglucon (Sandoz) intravenously, together with 5 cc. of Solu-B (Upjohn) at intervals, two to three times weekly, over a period of six to eight weeks.

This particular procedure of treatment is justified in the mechanism of calcium action, as set forth in the following observations:

(a) An increase in blood calcium leads (according to Hamburger,[16] Hooker,[17] Billingheimer,[18] Krogh,[19] and others) to increased tonus of capillaries and arterioles, and thus may counteract vasoparalytic vascular distention.

(b) A sequel to intravenous injections of therapeutic doses of calcium is stimulation of both divisions of the autonomic nervous system: *viz.*, a brief initial phase resembling vagal stimulation is followed by a second prolonged phase of sympathetic stimulation, whereby the sought-for therapeutic effects of calcium are put in operation.

These effects consist in cardiovascular stimulation, glycogen mobilization, increase in pulse rate and elevation of blood pressure (Barath,[20] Rothlin,[21] and Jansen[22]).

As demonstrated in the sensation of warmth which occurs during intravenous injections, calcium passes almost instantly from the blood into the tissues.

(c) The antispasmodic action of calcium has been established both experimentally and clinically.

The essential role played in the neuromuscular metabolism by vitamin B complex has been demonstrated repeatedly. Only a few pertinent points are mentioned in this connection:

Johnson and his co-workers[23] demonstrated that lack of vitamin B complex may cause fatigue and physical deterioration to an extreme degree.

It is well known that vitamin B complex, especially thiamin, is intimately related to the utilization of carbohydrates and the production of lactic acid. When Jolliffe[24] placed six physicians on a thiamin-deficient diet, the result was a uniformly extreme fatigue. Fatigue was replaced by a feeling of well-being when B_1 was restored to the diets of the physicians undergoing the experiment.

Therapeutic measures integrating treatment of multiple sclerosis include those aimed at combating increased fatigability and muscle weakness.

The relationship of the gonads to fatigue has been well established. Administration of sex hormones, it has been demonstrated, produces a sodium-potassium shift, accompanied by an increase in the positive nitrogen balance.

In a large percentage of the cases under discussion, encouraging reactions followed administrations of 1 to 2 cc. of 25 mgm. per cc. testosterone propionate (Oreton, Schering) three times weekly. The thrice-weekly intramuscular injections, numbering 30, were followed by sublingual administration of two 5 mgm. buccal Oreton tablets (Schering) daily for a period of six to eight weeks.

In a convincing majority of cases, increase in general strength, a sense of well-being, and considerable improvement in appetite were noteworthy.

For all patients a beneficial supplement to drug therapy comprised treatment procedures best summarized under the headings of (a) muscle re-education; and (b) psychotherapy.

Muscle Re-education

In the treatment of multiple sclerosis, muscle re-education or muscle rehabilitation has been recently advocated by Kabat,[25] Cailliet,[26] Rusk[27] and others.

According to my experience, however, the vigorous active-resistive type of muscle exercises, such as must be conducted by a physiotherapist, undertaken for periods of from one to two hours (Kabat,[25] Cailliet,[26]) are of questionable value in cases of multiple sclerosis.

Modified in form, the program of muscle rehabilitation advocated by the author is outlined as follows:

Inasmuch as most patients are too weak to cope with the ordinary physical functions which confront them daily as a matter of routine existence, regular muscle exercises are deliberately omitted from the initial phase of treatment.

Any additional physical demands made upon the patient are, in most cases, seemingly of such magnitude that those attempting to conform with a program of vigorous exercise are likely to meet with discouragement or, worse, may adopt an attitude of complete frustration.

As a precaution against these possibilities, patients are advised to postpone exercising until (under the effects of drug therapy) they are aware of improvement in general strength.

A system of mild exercising, worked out in accordance with individual needs based upon specific disabilities, is prescribed during the third or fourth week of treatment.

The patient is taught to exercise weak muscle, first without imposed resistance and, later, when muscle power increases, with resistance imposed. These initial exercise periods are scheduled only for five or ten minutes at hourly intervals.

As the patient continues to gain strength and its "by-product," personal confidence, physical exercises are given greater variety as well as more extended duration.

It is not possible here to discuss in detail the numerous types of muscle exercise devised for the strengthening of individual muscles, for the improvement of coordination, correction of difficulties in gait, and other disturbances of function.

A predominating disability in one or another case and varying patterns of disability in still other cases recommend careful consideration of each individual's needs and capabilities prior to prescription of muscle re-education routines.

Psychotherapy

Ranking in importance with drug therapy and muscle rehabilitation as aspects of management of multiple sclerosis, psychotherapy must be accorded its due as a factor making for success in the handling of patients (Langworthy).[28]

The essence of psychotherapeutic treatment of those afflicted with the disease is, in oversimplified terms, morale building.

The physician prejudiced against any remote possibility of furnishing assistance to the patient, more often than not, passes on to the patient his own attitude of distrust.

In similar fashion, the physician embarked upon an indiscriminate treatment program of "trying this, and then trying that," leads his patient ultimately into an attitude of hopelessness, a state of frustration the more shocking for him in contrast to his initial (and misplaced) confidence.

Frank pessimism on the part of the physician, though it relieves him of an unwanted burden of responsibility, inescapably plays havoc with the patient, as reflected in the latter's attitude of either negative acceptance of his plight or positive resentment bereft of any spirit to fight, or even compromise with, his disabilities.

In assuming the obligation to treat a patient afflicted with multiple sclerosis, the physician is confronted with the twofold responsibility of treating both the disease itself and the problems which the disease poses to its victims.

Multiple sclerosis should be interpreted to the patient as a not hopeless challenge to be met by the collaborative efforts of both physician and patient working as a team.

Results

In anticipation of whatever objections and criticism would hold true with respect to any proposed management of multiple sclerosis, several points require clarification.

Because of the frequent incidence of spontaneous remissions inherent in the nature of the disease, any and every beneficial result—or, rather, tendency to improvement or alleviation—must be appraised, not without a just proportion of skepticism.

Needless to say, observation of each case over a period of many years, if that were possible, would conform to the strictest of requisites and so would satisfy the most exigent critic.

Why so ideal a possibility lacks its counterpart in fact, except in the most rare instances, is acceptable without explanation.

These latter comments constitute a reasonable apology for the presentation of data which, accruing from personal experience in the treatment of multiple sclerosis, of necessity represents treatment periods falling distinctly short of the statistical ideal of two or three decades.

A gross evaluation of therapeutic results in a total of 237 cases is based upon an observation period varying from one to four years, a period during which patients were frequently subjected to complete reexaminations.

The series of cases fall into the following five subdivisions:

(1) Cases showing apparent complete recovery, without residual neurologic signs;

(2) Cases showing partial recovery, with measurable improvement in the neurologic findings;

(3) Cases displaying partial recovery, limited to subjective complaints but without objective neurologic changes:

(4) Cases that failed to show improvement, but did remain stationary; and

(5) Cases in which the disease displayed a progressive downhill course.

If any conclusions are to be drawn from the statistical data to be presented herewith they must be "watered down" in light of the fact that (as the writer has carefully pointed out) treatment periods for the 237 cases under consideration were as short, in some instances, as one year and, in other instances, never longer than four.

Of the total number, 237 cases, apparent complete recovery was noted in 35 cases (14.8 per cent).

Partial recovery accompanied by some improvement of the neurologic signs was observed in 121 cases (51.05 per cent).

Subjective improvment without objective neurologic changes was observed in 57 cases (24.05 per cent).

Cases termed stationary, inasmuch as they showed neither improvement nor disease progression, numbered 22 (9.3 per cent).

Two cases (0.8 per cent) displayed a continuous downhill course.

The statistical figures show, in summary, that among 237 patients who underwent treatment for various periods ranging from one to four years, 157 (66.3 per cent) showed either complete or partial recovery with respect to both subjective and objective signs of improvement; 57 (24.05 per cent) improved only slightly and without evidence of neurological changes; and 24 cases were complete failures.

Spontaneous remissions, according to the writer's experience, are by no means characteristic of *all* cases of multiple sclerosis. There are cases which display a typical remissive course, and there are other cases characterized by steady, unremitting progression of the disease.

If this differentiation is valid, as the writer believes, then any objective evaluation of treatment of multiple sclerosis must be based upon the record of achievement or failure of treatment as applied *solely to a group of patients afflicted with the progressive form of the disease*, ruling out the possibility of spontaneous remissions.

It is of interest to note, in this connection, that among the 250 patients comprising the original total of cases under observation, only 96 (38.4 per cent) so far as the observer was able to ascertain through investigation, were of the type displaying remissable phenomena, whereas the remaining 154 (61.6 per cent) produced evidence of the progressive form of the disease, uninterrupted by any known remissive intervals.

An additional statistical breakdown limited to the progressive *nonremittant* type is accordingly of significance:

Of 237 *treated* patients, 141 revealed a *steadily progressive course* without remission. In this group of 141, 17 (12 per cent) showed apparent complete recovery; 68 (48.2 per cent) showed partial recovery both subjectively and in improvement of their neurologic findings: 34 (24.1 per cent) revealed subjective improvement only, and 22 (15.6 per cent) were complete failures.

In summary, statistical figures show that, of these 141 cases having progressive characteristics, 85 showed either complete or partial recovery; 34 improved only slightly and without evidence of neurologic changes; and 22 were complete failures.

Noteworthy also, in the writer's view, is the fact that a marked plurality of cases undergoing treatment revealed degrees of improvement closely related to, or in actual parallelism with, arterial blood pressure levels.

Conclusions

The *early* stages of multiple sclerosis lesions and their relation to vascular disturbances were studied. A positive correlation was found between the early stage of plaque formation and the presence of vascular abnormalities.

The view is expressed that vascular changes, particularly vasoparalysis of small blood vessels associated with stasis and congestion, are an essential factor in the pathogenesis of multiple sclerosis.

A clinical study of 250 cases of multiple sclerosis yielded the following pertinent observations:

(a) Present in 152 cases (61.6 per cent) the frequency of a striking increased fatigability of skeletal muscles is given emphasis.

(b) Repeated measurements of arterial blood pressure revealed a total of 134 patients (53.6 per cent) providing evidence of *low* blood pressure.

(c) Therapeutic measures based upon the author's concept of the pathogenesis of the disease are described under the general headings of drug therapy, muscle rehabilitation, and psychotherapy.

(d) Various vasopressor drugs are recommended in treatment as agents to counteract vasoparalysis of the small blood vessels of the central nervous system and to effect elevation of arterial blood pressure.

(e) In cases showing improvement following treatment, the degree of improvement appeared closely related to, or in actual parallelism with, arterial blood pressure levels.

A series of 237 cases of multiple sclerosis furnished material for observations concerning treatment.

Of the 237 patients treated for periods ranging from one to four years, 157 (66.3 per cent) showed either complete or partial recovery with respect to both subjective and objective signs of improvement; 57 (24.05 per cent) improved only slightly and without evidence of neurologic changes; and 24 cases were complete failures.

Of 250 cases under investigation, only 96 (38.4 per cent) displayed a remittent clinical course, considered typical of the disease. The other 154 cases (61.6 per cent) provided evidence of a *steadily progressive nonremittent* form of multiple sclerosis.

For a better evaluation of the results of treatment, ruling out the possibility of confusing spontaneous remissions with improvement following therapy, 141 treated cases characterized with a steadily progressive clinical course were analyzed, providing the following statistical data: 85 showed either complete or partial recovery; 34 improved only slightly and without evidence of neurologic changes; and 22 were complete failures.

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Part II. Biochemical Methods

PAPER CHROMATOGRAPHY OF THE AMINO ACIDS OF CEREBROSPINAL FLUID

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A considerable part of this report will deal with the development of a paper chromatographic method for analyzing cerebrospinal fluid since, although partition chromatography is in wide usage presently, its theoretical background is not such as will allow of predictable behavior on the part of a given biological fluid. A specific analytic problem is thus better attacked at the bench than in the library.[1]

References to the paper chromatographic separation of free amino acids and other biological substances in tissue, blood, and urine are numerous in the literature, but there has been little work published on the amino acids of cerebrospinal fluid. A microbiological assay of the fluid has yielded considerable information as to which amino acids should be expected.[2] This information provided the basis for preparing the synthetic spinal fluids which were here utilized for establishing the qualitative and quantitative attack upon the present problem.

One report[3] has appeared in which the single amino acid *alanine* has been studied by paper chromatographic methods in normal and pathological fluids, including two cases of multiple sclerosis. No notable conclusions were drawn.

Reagents and Apparatus

Apparatus.

Tanks. Two large cylindrical glass tanks approximately 50 by 20 inches were used for running the chromatograms.

Paper. Filter paper of Whatman grade No. 1 was used for all chromatograms.

Ultraviolet lamp.

Water bath. For a water bath a shallow Pyrex dish, 14 by 3 by 6 inches, was supported on two ring stands and heated by two Bunsen burners. These burners proved sufficient to keep a rack of 28 tubes at approximately 100° C. for 20 minutes.

Drying oven. An incubator equipped with a thermostat was used for drying the chromatograms between runs. The temperature was kept at 40° C., since higher temperatures cause a loss of amino acids when phenol is being removed from the paper.

Electric oven. An electric oven was used to bring out the spots after spraying the dry chromatograms with a dilute (0.1 per cent) ninhydrin solution. This oven should be kept at approximately 100° C., and 5 to 10 minutes was found to be sufficient length of time for color development of all spots.

Spectrophotometer. A Coleman Junior Spectrophotometer, Model 6, was used for all readings.

Test tubes and racks. Pyrex tubes 30 by 150 mm. without lips were used throughout the test. These tubes were calibrated to 10 ml. for constant dilution. For all photometric readings, Coleman Cuvettes (Type B) were used. These tubes were not individually calibrated.

Atomizer. For ninhydrin spraying an atomizer was constructed out of a 250-ml. Erlenmeyer flask and glass tubing.

Pipettes. Regular 0.2-ml. serological pipettes calibrated to 10 microliters were used for the initial qualitative work. For more accuracy in quantitative work, hemoglobin pipettes calibrated to 20 microliters were used. The narrower tips on these pipettes proved quite satisfactory for spotting the papers. By means of these pipettes it was possible to get spots ½ cm. in diameter with reasonable consistency.

Hair dryer. A hair dryer was found useful in drying the spots as they were applied to the paper. This greatly cut down the amount of time necessary for applying the standards and unknowns to the paper while keeping the spots as small as possible.

Reagents.

Amino acids. Amino acids for standards were obtained from Nutritional Biochemicals and were used without further purification. Standard solutions of amino acids were made up .01 *M* in distilled water. These were autoclaved in plasma bottles and kept under sterile conditions. An improvement over this would have been the use of ethyl alcohol as a solvent, thereby making unnecessary any particular procedures to assure sterility.

Solvents. Phenol: Regular reagent grade Merck phenol was purified by distillation before use. The commercial reagent was found to contain a slight yellow coloration which was undesirable.

Methyl cellosolve: The commercial reagent was distilled before use, and was employed for a second dimension solvent on many of the chromatograms.

n-Propanol: This reagent was obtained as the commercial product, and it was not found necessary to purify it.

Diluents. As a dilutent in the Moore and Stein[4] photometric method a 1:1 n-propanol-water was used.

Citrate buffer. A citric acid buffer of pH 4.95 was prepared by weighing out 21.01 grams of citric acid, adding 200 ml. of 1 *N* NaOH, and diluting to 500 ml.

Ninhydrin solutions. A 0.2 per cent solution of ninhydrin in water and later a .1 per cent ninhydrin solution in butanol saturated with water was used.

Quantitative ninhydrin solution: The Moore and Stein quantitative ninhydrin solution was made up as follows: 0.8 grams of reagent $SnCl_2 \cdot 2H_2O$ in 500 ml. of citrate buffer (pH 5) was added to 20 grams of ninhydrin dissolved in 500 ml. of methyl cellosolve.

Ammonia water was used to get better resolution of the basic amino acids in phenol. Four drops were added to the inside of the tank before each run in phenol.

Hydrocyanic acid was tried for getting rid of the "pink beard" in the phenol runs. Sufficient concentration of HCN was maintained during the run by adding KCN to the solvent. Its effect on R_f values, however, caused the abandonment of its use.

Procedures

In preparing chromatograms of known amino acids for reference purposes, 0.2 ml. portions of the standard solutions or of mixtures thereof, containing 2.8 micrograms of alpha-amino nitrogen, were spotted on the paper at approximately 4 cm. intervals. The paper was rolled into a cylinder, stapled, and placed on its spotted edge into a tank, at the bottom of which was a petri dish containing phenol and water (80:20). The solvent was allowed to climb for 16 hours, reaching a height of approximately 30 cm.

For examination under ultraviolet light, the chromatogram was dried at 100° C. for 35 minutes. The distance from the base line of each fluorescing spot is measured, and the ratio of this distance to the distance traveled by the solvent front is the R_f value.[5] In order to secure R_f values corresponding to those reported for the basic amino acids by Dent,[6] it was found necessary to add ammonia as described above.

The R_f values obtained from one-dimensional chromatograms were used for the location and identification of amino acids on the two-dimensional papers. After permitting a spreading of the amino acids according to their R_f's along the phenol edge, the chromatogram was dried and made into a new cylinder with the partially spread amino acids parallel to the surface of the second solvent. The chromatogram was developed in the manner already described.

A synthetic spinal fluid was made up on the basis of published microbiological analysis,[2] containing the following amino acids: beta alanine, alpha alanine, arginine, aspartic acid, cystine, glutamic acid, leucine, histidine, lysine, ornithine, phenylalanine, proline, serine, threonine, tyrosine, valine, glycine, gamma-amino-butyric acid, and glutamine. By using phenol as the first solvent, and methyl cellosolve for the second solvent, reproducible two-dimensional chromatograms were obtained with this synthetic fluid.

For quantitative estimations, standard tubes for each acid were set up containing 2.8, 5.6, and 8.4 micrograms of alpha-amino nitrogen. One-dimensional chromatograms were developed in Propanol-water (80:20) as the solvent. They were air-dried and sprayed with 0.1 per cent ninhydrin solution in butanol saturated with water. The papers were then placed in the electric oven for five minutes to allow color development of the spots. The spots were circled, cut out from the paper, and set into test tubes for elution. A representative spot was cut out from the paper to serve as a blank.

To each test tube containing the filter paper 3 ml. of distilled water were added. The tubes were then immersed in a bath of boiling water for 1½ hours. After completing the elution, 2 ml. of the Moore-Stein ninhydrin reagent were added in citrate buffer (pH 5) to each of the unknown and standard tubes. All tubes were then immersed in a bath of vigorously boiling water for 20 minutes to allow full color development. The tubes were then removed, cooled slightly, and brought up to a volume of 10 ml. with a sufficient amount of n-Propanol-water (1:1) diluent. Per cent recovery was determined by comparing the optical densities of the eluted amino acids with the optical densities of the corresponding standard tubes.

Desalting of spinal fluids. Since the ions of the inorganic salts of biological fluids move characteristically during the development of the chromatogram,[7] the application of the chromatographic method on untreated biological fluids for amino acids present in only trace amounts is inadequate.[8] The inorganic ions would come to occupy large areas of the paper finally "shouldering off" the amino acids, causing them to appear as distorted streaks surrounding parts of the salt areas. For example, glutamine, glutamic acid, and aspartic acid are noticeably affected in this way.

There is now a method for prior removal of most of the salts,[9] which can be readily adapted to from 1 to 10 ml. of solution. The apparatus consists essentially of a funnel through which mercury is circulated by a water lift pump. The solution to be desalted floats on the mercury into which dips the graphite anode which is enclosed in a cellophane bag containing 0.1 N H_2SO_4. This membrane permits the passage of anions of strong electrolytes to the anode, while hydrogen ions pass in the opposite direction.

The amino acids, including the dicarboxylic acids, acquire a net positive charge within the membrane and are thus less likely than are uncharged molecules to reach the anode compartment. The mercury cathode discharges hydrogen ions and other inorganic cations, hydrogen being liberated, and the metals dissolve in the mercury. These metals are washed out of the mercury by the pump water. As the concentration of the solution falls, the resistance of the apparatus rises and the current falls. This small, steady value can be used to determine the end point of the desalting process.

To test the apparatus for amino acid loss, either by its passing into the anode compartment or by being carried away in droplet form by the mercury, standard solutions of amino acids were made up in physiological saline and desalted. The color which was developed by the amino acids in the desalted fluid was then compared photometrically with the standards which were not desalted. No loss in excess of 5 per cent was detected.

Dent states that after "desalting" in this manner, over 3 ml. of cerebrospinal fluid can be analyzed satisfactorily on one chromatogram, even though the original fluid gave distortions when only 0.1 ml. was used.[8] This procedure provides a method, therefore, for the detection of amino acids in concentrations as low as 1 mgm. per ml.

Preparation of spinal fluids for chromatography involves the following steps:

(1) All cellular debris is spun down for 15 minutes in a refrigerator centrifuge;

(2) To the supernatant is added 5 volumes of EtOH for protein precipitation;

(3) The solution is then centrifuged at 2000 rpm. to bring down the protein;

(4) The supernatant is brought down to dryness on a steam bath;

(5) The residue is taken up in 10 ml. of distilled water;

(6) This solution is then desalted by means of the "desalting" apparatus; and

(7) The "desalted" solution is then brought down to dryness on a steam bath. This final residue is then dissolved in approximately 0.25 ml. of distilled water and spotted on a chromatogram.

Results

Application of the procedures described yielded results which are summarized in the following statements, omitting details of preliminary experimentation:

(1) Separation of the amino acids in cerebrospinal fluid can be reproducibly achieved by the use of phenol-water (80:20), with ammonia, as described, as the first solvent, and Propanol-water (80:20) as the second solvent. Lutidine-methyl cellosolve-water (90:90:60) can be used in place of Propanol-water.

(2) On the basis of such separation, identification of the amino acids can be made. Recognition is given here to the fact that the most positive identification lies in the elution of the spots and running them in a third solvent in order to confirm the R_f values in the solvent against standard solutions of known amino acids. This more rigorous method of identification was by-passed in favor of the single two-dimensional chromatogram.

(3) The adequacy of the desalting apparatus was firmly established. Solutions were desalted to the point wherein no precipitate was observed upon the addition of a 1 per cent solution of silver nitrate. It was also shown that the desalting process caused no loss of amino acids in excess of 5 per cent.

(4) In the application of the quantitative procedure as described, reproducible low results were obtained. The effects of spotting, heating, drying, and elution were studied individually and shown not to cause any significant loss in recovery attempts. The chief loss seems to occur in the development of the chromatogram with the solvents used. Compensation for this loss can be made by correction. In their quantitative procedure, McFarren and Mills[10] compare the density of unknown spots in the chromatogram with spots similarly developed from standard solutions. Their results were reproducible and precise.

(5) The amino acids of cerebrospinal fluid which were consistently identified may be summarized as follows: alpha-alanine, aspartic acid, glutamic acid, phenylalanine, serine, valine, glycine, gamma-amino-butyric acid, and glutamine. Less constantly one finds: arginine, leucine, lysine, ornithine, threonine. Still less frequently one finds proline and tyrosine. Furthermore, proline seems to be present in only those fluids which have high protein values. The questionable presence of cystine, hydroxyproline, alpha-amino-butyric acid, glutathione, glucosamine, methionine sulfoxide, and taurine are included for the sake of completeness. The identification of gamma-amino-butyric acid serves to confirm the report of its presence in the cerebrospinal fluid by Gilligan *et al.*[11] Of interest also is the fact that histidine, which was reported by Solomon *et al.*[2] to be in the cerebrospinal fluid, could not be demonstrated in the present investigation. This may very well be owing to the fact that histidine gives less color development per microgram of amino acid than most of the other acids

present in the cerebrospinal fluid. In contrast, the presence of proline was definitely shown in at least three of the reported fluids and was noted in at least four other fluids which were simultaneously investigated. This finding is to be compared with the results of Solomon *et al.*,[2] who were unable to demonstrate the presence of proline by their microbiological technique.

We have not had opportunity to attempt the confirmation of the finding of histamine[12] in cerebrospinal fluids, since the report came to our hands only recently.

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Discussion of the Paper

Doctor Pinckney J. Harman *New York University-Bellevue Medical Center, New York, N. Y.:* I am very grateful for the opportunity of opening the discussion of Doctor Walker's very interesting paper, especially since we ourselves have been studying free amino acids in neural tissues and fluids by chromatography for several years. These studies have also included observations on human cerebrospinal fluids. During the past year Mrs. Crouch has been working with material supplied us by Doctor Nathanson's group in neurology at Bellevue, and we have standardized a procedure quite similar to that of Doctor Walker's group. Our first concern after the technical difficulties had been overcome was the question of a normal pattern, and we have obtained evidence of a consistent pattern in an apparently normal group who were relieved of spinal fluid in conjunction with anesthesia, although this number is not yet large. In a small number of other patients the only deviations so far noted, in fact, have been in individuals having marked metabolic or neurologic involvement. Although we are accordingly still in the preliminary stages, the possibility of deviants of diagnostic value has not yet been ruled out and has some promise. Our patterns agree qualitatively at least in most respects with Doctor Walker's with two exceptions: (1) We consistently find leucine as well as valine. He does not. (2) He consistently finds gamma aminobutyric acid. We do not. The discrepancy about leucine might be related to its proximity to valine, but I am at a loss to explain the absence of gamma aminobutyric acid in our papers. Furthermore, I believe this difference is important since this amino acid is a consistent constituent of the central nervous system and since we have adduced evidence that it is importantly related to the central gray matter. Our technique has been dilution of 4 cc. of spinal fluid with 8 cc. of absolute ethanol with subsequent treatment identical to Walker's, except that we use Block's lutidine-ethanol-water mixture as a second solvent instead of Propanol-water. We find gamma aminobutyric consistently in brain and spinal cord homogenates, but have never detected it in 20-odd spinal fluid analyses. We have occasionally found beta alanine and even suspected histidine in spinal fluid, but our experience with gamma aminobutyric acid has been so sufficiently extensive that we feel we can rule out the possibility of confusion with these compounds.

PROTEIN FRACTIONS IN SERUM AND CEREBROSPINAL FLUID IN MULTIPLE SCLEROSIS

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That changes occur in the protein composition of the cerebrospinal fluid of patients having multiple sclerosis is now well known.[1] This fact is shown not only by the chemical results obtained with such qualitative or semiquantitative procedures as the colloidal gold reaction of Lange,[2, 3] but also by the more recent quantitative studies of Kabat and his co-workers[4] employing immunochemical methods. It is not generally known, however, that these spinal fluid changes are also accompanied by definite changes in the protein composition of the blood serum of patients afflicted with multiple sclerosis. Such positive findings have been reported in recent years employing qualitative and semiquantitative tests such as the thymol-turbidity reaction,[5] by paper chromatography as reported by Swank, Franklin, and Quastel[6] and by a quantitative cephalin flocculation reaction with temperature variations which shows abnormal serum patterns for multiple sclerosis cases which resemble those found in liver disease.[7, 8] Because of these suggestive findings a study was undertaken of serum protein changes in multiple sclerosis using more of a quantitative approach, namely the electrophoretic method.[9] The results obtained by this technique were compared with the quantitative protein flocculation procedures developed in our laboratory[10, 11] as well as with a number of the well-known qualitative protein flocculation reactions such as the cephalin-cholesterol flocculation reaction, the thymol-turbidity test, the zinc-sulfate turbidity method, and the ammonium sulfate-sodium chloride turbidity method.

Recently the protein flocculation-ninhydrin procedure developed for serum gamma globulin in this laboratory has been applied to the determination of the gamma globulin content of the cerebrospinal fluid[12] in comparison with the immunochemical method of Kabat.[4] These simple quantitative protein flocculation methods make it feasible to study, on a routine basis, the gamma globulin values of both serum and cerebrospinal fluid of cases of various neurological disorders, including multiple sclerosis.

It is thus hoped to develop laboratory data which may aid the clinician in making the frequently difficult diagnosis of multiple sclerosis and help in the differentiation of this condition from other neurologic diseases of similar symptomatology.

Methods and Procedures

(A) *Selection of Patient Material.* The patients studied were carefully selected according to the diagnostic criteria for multiple sclerosis as previously defined by Schumacher.[13]

(B) *Serum Determinations:*

(1) *Electrophoretic Procedure.* The methods used for electrophoretic studies have been fully described in a previous publication.[9] A typical electrophoretic

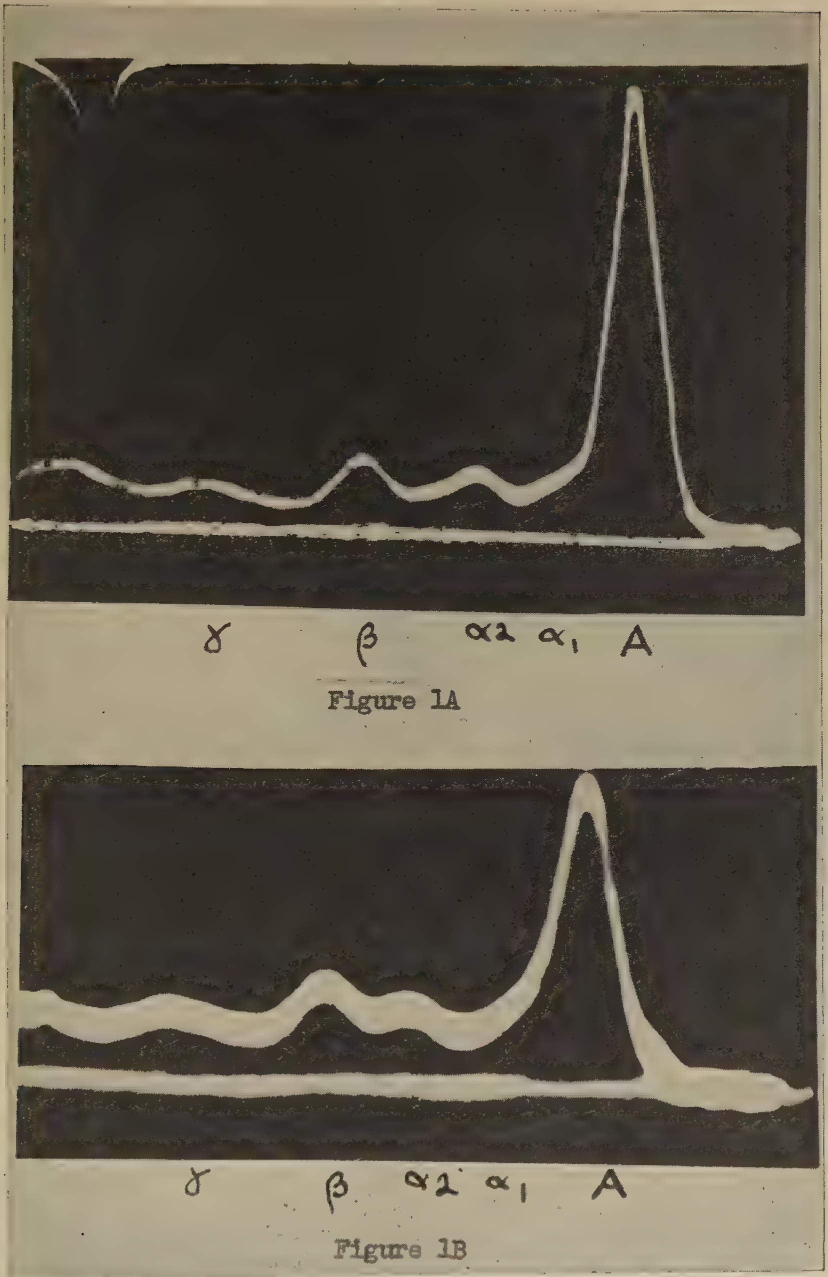

FIGURE 1. (1A) Electrophoretic pattern for normal serum. (1B) Typical electrophoretic pattern for serum from a case of multiple sclerosis (note the increased area under the beta and alpha-2 globulin peaks and the decreased area under the albumin peak).

TABLE 1

SUMMARY OF ELECTROPHORETIC DATA FOR SERA FROM MULTIPLE SCLEROSIS CASES

Electrophoretic Data

No. of cases	Albumin gm./100 cc.	Alpha-1 gm./100 cc.	Alpha-2 gm./100 cc.	Beta gm./100 cc.	Gamma gm./100 cc.
	Mean S.D.†	*Mean S.D.*	*Mean S.D.*	*Mean S.D.*	*Mean S.D.*
Multiple sclerosis sera (23)	3.57 ± .37	0.49 ± .11	0.80 ± .18	1.34 ± .24	1.12 ± .17
	Range	*Range*	*Range*	*Range*	*Range*
	2.72–4.52	0.34–0.80	0.44–1.24	0.94–1.86	0.68–1.45
	Mean S.D.	*Mean S.D.*	*Mean S.D.*	*Mean S.D.*	*Mean S.D.*
Normal sera* (80)	4.3 ± .33	0.5 ± .11	0.6 ± .17	0.9 ± .27	1.0 ± .21

* Electrophoretic data for normal sera from paper by Reiner, Fenichel and Stern.[19]

† 1 S.D. $\simeq$ 3 S.E. The standard error (S.E.) is used for the comparison of the means of two series, *i.e.*, normals and multiple sclerosis.

pattern obtained with serum from a case of multiple sclerosis as compared with that for a normal individual is shown in FIGURE 1.*

(2) *Qualitative Serum Protein Flocculation Procedures.* Tests used in these studies included the cephalin-cholesterol flocculation procedure of Hanger,[14] the thymol-turbidity reaction test of Maclagan,[15] the zinc-sulfate turbidity reaction of Kunkel[16] and the ammonium sulfate-sodium chloride turbidity test of de la Huerga and Popper.[17]

(3) *Quantitative Protein Flocculation Procedures.* The photometric flocculation-ninhydrin procedure used in these experiments for the quantitative determination of serum gamma globulins and for the total serum/gamma globulin ratio values, and their chemical and clinical significance have been discussed in previous publications from this laboratory.[10, 11]

The quantitative cephalin-cholesterol flocculation reaction developed by Saifer[18] together with temperature variation[7, 8] was employed to determine the serum protein patterns for cases of multiple sclerosis.

(C) *Cerebrospinal Fluid Determinations. Quantitative Protein Flocculation-Ninhydrin Method for Gamma Globulin.* The procedure used in this study has been described in a recent publication.[12] In a series of 100 neurological cases this simple chemical method was found to check closely with the values obtained by the immunochemical method of Kabat[4] as performed in his laboratory.

Results and Comments

(A) *Serum.* The electrophoretic procedure previously described was carried out on the sera of the 23 selected cases of multiple sclerosis. In addition normal sera were run as control studies under identical conditions. Since the instrument used in our studies was of a design similar to that employed by Reiner, Fenichel, and Stern,[19] their larger series of 80 cases was used in performing the statistical analysis in our study. The mean values, standard deviations, and the range of values obtained for these 23 selected cases of multiple sclerosis,

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* FIGURES 1A and 1B are from Saifer *et al.*[9]

TABLE 2

DISTRIBUTION OF ELECTROPHORETIC PROTEIN FRACTIONS OF SERA FROM MULTIPLE SCLEROSIS CASES

Protein fraction	Electrophoretic values gm. per 100 cc. serum					% of cases at least 1 S.D. removed from normal mean value
Albumin	2.95–3.28	3.29–3.62	3.63–3.96	3.97–4.30*	4.31–4.64	$\frac{20}{23}$ = 87%
No. of cases	5	9	6	2	1	
Alpha-2-globulins	0.43–0.60*	0.61–0.78	0.79–0.96	0.97–1.14		$\frac{15}{23}$ = 65%
No. of cases	2	6	12	3		
Beta globulins	0.90*–1.17	1.18–1.45	1.46–1.73	1.74–2.01		$\frac{17}{23}$ = 74%
No. of cases	6	11	4	2		
Gamma globulins	0.58–0.79	0.80–1.00*	1.01–1.22	1.23–1.44		$\frac{6}{23}$ = 26%
No. of cases	1	4	12	6		
A/G ratio	0.62–0.78	0.79–0.95	0.96–1.12	1.13–1.29*		$\frac{20}{23}$ = 87%
No. of cases	3	8	9	3		

* Mean value for normal sera. All the values in this table are grouped in terms of the standard deviation (S.D.) from this mean value as given in TABLES 1 and 5 for each component.

as compared to the values obtained for normal sera, are given in TABLE 1.* It is evident from FIGURE 1B and TABLE 1 that there is a markedly lowered albumin and A/G ratio and increased beta and/or alpha-2 globulin values. The alpha-1 globulin fractions fall within the normal range, but the gamma globulin level is usually slightly elevated above the normal mean value for this component. The statistical analysis of these electrophoretic data are more clearly shown in TABLE 2, where the 23 cases are divided into groups for each protein fraction on the basis of the number of standard deviations a particular value deviates from the mean value for that component. Those values are considered as abnormal which deviate at least one standard deviation from the mean value of that component, since for the group 1 S.D. $\cong$ 3 S.E. (standard errors). The number of cases showing abnormal values for each protein fraction, expressed in percentage figures, is shown in the right column of TABLE 2.

The electrophoretic data in TABLE 2 demonstrates that about 85 per cent of the patients studied showed similar abnormalities in their serum proteins. Of the remaining 15 per cent, most patients showed abnormalities of some, but not all of these protein fractions.

Since the electroporetic technique of serum protein fractionation is expensive, time consuming, and impractical for routine clinical analysis, the simpler qualitative and quantitative protein flocculation reactions were studied in the sera of the same 23 cases of multiple sclerosis (*cf.* TABLES 3 and 4).

The data in TABLE 3 show that the greatest number of positive tests (66 per cent) is given by the cephalin-cholesterol flocculation reaction of Hanger.[14] As suggested by Hanger[20] this reflects changes in the electrophoretic albumin

* TABLES 1 to 4 inclusive are from Saifer *et al.* TABLES 5 and 6 are from Saifer and Narby.[12]

TABLE 3

QUALITATIVE PROTEIN FLOCCULATION DATA FOR SERA FROM MULTIPLE SCLEROSIS CASES

No. of cases	Thymol turbidity* units	Zinc sulfate turbidity* units	Ammonium sulfate sodium chloride turbidity* units	Cephalin-cholesterol flocculation 24 hour reading
Multiple sclerosis (23)	*Mean S.D.* 1.6 ± .9 *Range* 0.5–4.4 *% above normal* 29%	*Mean S.D.* 4.4 ± 1.5 *Range* 1.1–6.8 *% above normal* 21%	*Mean S.D.* 1.9 ± .75 *Range* 0.7–3.3 *% above normal* 8.3%	*Mean S.D.* 1–2+ *Range* 0–4+ *% above normal* 66%
Normal sera†	0–2	1–6	1.2–3	0– ±

* Turbidity values in this table are all expressed in Maclagan units (1947. Brit. Med. J., **2:** 197.) and should be multiplied by two to conform to the commonly used Shank and Hoagland units (1946. J. Biol. Chem., **162:** 133.)

† Normal values listed in this table are those established by the originators of the methods used and then confirmed in our routine biochemical laboratory.

fraction. Similar changes in protein composition were shown by the more sensitive quantitative cephalin-cholesterol flocculation reaction with temperature variations as developed by one of us.[7, 8] This quantitative procedure gave positive findings in about 88 per cent of the multiple sclerosis cases tested. The thymol turbidity reaction of Maclagan[15] also gave positive findings in about 29 per cent of our series of multiple sclerosis cases. As pointed out by several investigators this test reflects changes in the beta globulin fraction which is markedly increased electrophoretically. The zinc sulfate turbidity test of Kunkel[16] and the ammonium sulfate-sodium chloride turibidity test of de la Huerga and Popper,[17] which reflect mainly changes in the gamma globulin fraction show the smallest percentage increase above normal for the multiple sclerosis cases. This indication would be in agreement with the electrophoretic findings in which either a normal or slightly elevated gamma globulin level is found in this disease.

TABLE 4

QUANTITATIVE PROTEIN FLOCCULATION DATA FOR SERA FROM MULTIPLE SCLEROSIS CASES

No of cases	Total serum gamma globulin gm. per 100 cc.	Globulin clot-gamma globulin gm. per 100 cc.	Gamma globulin electro-phoretic gm. per 100 cc.	Total serum / globulin clot	Electro-phoretic beta + gamma / gamma
Multiple sclerosis (23)	*Mean S.D.* 1.74 ± .19 *Range* 1.37–2.10	*Mean S.D.* 1.13 ± .19 *Range* 0.92–1.44	*Mean S.D.* 1.1 ± .17 *Range* 0.7–1.5	*Mean S.D.* 1.55 ± .19 *Range* 1.20–1.86	*Mean S.D.* 2.21 ± .22 *Range* 1.94–3.05
Normal sera (32)	*Mean. S.D.* 1.54 ± .23 *Range* 1.09–2.00	*Mean S.D.* 1.00 ± .13 *Range* 0.72–1.25	*Mean S.D.* 1.0 ± .21 *Range* 0.8–1.2	*Mean S.D.* 1.55 ± .12 *Range* 1.40–1.83	*Mean S.D.* 1.9 ± .24 *Range* 1.5–2.2

The quantitative protein flocculation methods as developed in this laboratory[10, 11] give data which, as shown in TABLE 4, illustrate the close correspondence between the electrophoretic results for serum gamma globulin as compared with those obtained with this simple photometric method. The increase in the total serum-gamma globulin values shown in this table reflects changes for this disease in the beta as well as in the gamma globulins, as is found with the electrophoretic method. The data obtained with these simple qualitative and quantitative protein flocculation tests, in general, confirm the changes found with the electrophoretic method but give positive results in a smaller percentage of the cases studied.

(B) *Cerebrospinal Fluid.* As previously mentioned, changes in the protein composition of the cerebrospinal fluid of patients afflicted by multiple sclerosis have been determined, qualitatively or semiquantitatively, with the colloidal gold reaction of Lange[2, 3, 21] in most clinical laboratories. That a positive colloidal gold reaction is caused by an increase in the globulin fraction, a decrease in the albumin fraction, or both, has been known from the work of Kafka and his co-workers[22, 23] employing salt fractionation methods. More recent work with the electrophoretic technique[24, 25] has confirmed the earlier work of Kafka as to particular protein fractions responsible for the changes observed with the colloidal gold reaction. These electrophoretic studies of the cerebrospinal fluid in disease cases[25, 26, 27] as compared to normal individuals, showed that the major changes occur in the albumin, beta globulin, and the gamma globulin fractions. The increase in the albumin fraction in pathological conditions follows closely the total protein value,[28] whereas the increase in the beta and gamma globulin fractions may be indicative of an antibody response.[25] Although the electrophoretic method gives a quantitative distribution of protein fractions present in the cerebrospinal fluid it is impractical as a clinical procedure because of the large volumes of fluid required and the complexities of the analysis. This need for a practical quantitative measure of the protein frac-

TABLE 5

COMPARISON OF QUANTITATIVE PROTEIN FLOCCULATION-NINHYDRIN AND IMMUNOCHEMICAL METHODS FOR CEREBROSPINAL FLUIDS FROM NEUROLOGICAL CASES

C.S.F. no.	Tot. protein mgm./100 ml.	Protein flocculation-ninhydrin gamma globulin mgm./100 ml.	Immunochemical gamma globulin mgm./100 ml.	Difference mgm./100 ml.	Gamma glob. / T.P. %
1	83	14.2; 14.4; 14.0 Average = 14.2	14.9	−0.7	18.0
2	85	0.81; 0.83; 0.90 Average = 0.85	0.70	+0.2	0.8
3	54	4.1; 4.1; 4.0 Average = 4.1	4.1	±0.0	7.6
4	49	5.0; 4.8; 4.5 Average = 4.8	4.3	+0.5	8.8
5	62	8.0; 8.4; 8.0 Average = 8.1	8.3	−0.2	13.4
6	46	5.0; 5.4; 5.6 Average = 5.3	4.6	+0.7	10.0

S.D. = ±.18 mgm./100 ml. Normal range 2–6 mgm. gamma globulin/100 ml. Normal gamma globulin/total protein ratio = 5.7 to 13.0.

tions, *e.g.*, albumin, gamma globulin, *etc.*, present in the cerebrospinal fluid led to the application of immunochemical techniques by Kabat and his co-workers[4, 28, 29] to this problem. These workers showed that 85 per cent of a series of 100 cases with multiple sclerosis had either an increased gamma globulin value above normal or an increased gamma globulin/total protein ratio in their cerebrospinal fluid. While the importance of these clinical findings should not be minimized, the use of this method for most clinical laboratories encounters difficulties, as stated by Merritt,[30] because of the involved preparation and assay of the antisera used and the time-consuming analytical technique required.

Recently a simple photometric method was elaborated in this laboratory for the quantitative determination of the gamma globulin content of cerebrospinal fluid based on a protein flocculation-ninhydrin reaction.[12] This procedure checks closely with the immunochemical method of Kabat[4] over a wide range of values, requires only 1 ml. of cerebrospinal fluid per determination, and permits large numbers of determinations to be performed daily. By the use of this simple quantitative technique which is suitable for routine clinical analysis, the findings of Kabat, *et al.*[28] were confirmed in that about 80 per cent of our series of 23 cases showed increased gamma globulin values in the cerebrospinal fluid.

The reproducibility of this method is shown by the data in TABLE 5 which presents the results of triplicate determinations. In addition, the mean value checks very closely, *i.e.*, within ±1 mg. per cent, with the values obtained by means of the immunochemical method as performed in Doctor Kabat's laboratory. Recoveries of added gamma globulin to cerebrospinal fluid were obtained with an average error of ±5 per cent.

This procedure was applied to a series of 100 cerebrospinal fluids selected at random from patients suffering from various neurological disorders and compared with the immunochemical procedure as seen from the data in TABLE 6.

TABLE 6

DISTRIBUTION OF GAMMA GLOBULIN VALUES FOR 100 CEREBROSPINAL FLUIDS* FROM NEUROLOGICAL CASES AND COMPARISON OF RESULTS OBTAINED WITH THE IMMUNOCHEMICAL AND PROTEIN FLOCCULATION-NINHYDRIN METHODS

	Gamma globulin—mg. per 100 ml.											
	0–1.0	1.1–2.0	2.1–3.0	3.1–4.0	4.1–5.0	5.1–6.0	6.1–7.0	7.1–8.0	8.1–9.0	9.1–10.0	10.1–12.0	12.0–20.0
No. of cases	1	3	12	8	18	9	18	6	5	4	12	4
Flocculation-ninhydrin (mean)	0.7	1.7	2.6	3.5	4.5	5.7	6.5	7.5	8.4	9.2	11.1	14.8
Immunochemical (mean)	1.1	2.4	2.5	3.1	4.1	5.4	6.2	7.3	8.4	8.6	11.4	14.1

* The total protein values for this series as determined by the Denis and Ayer method ranges from 21 to 118 mg. per 100 ml. of spinal fluid.

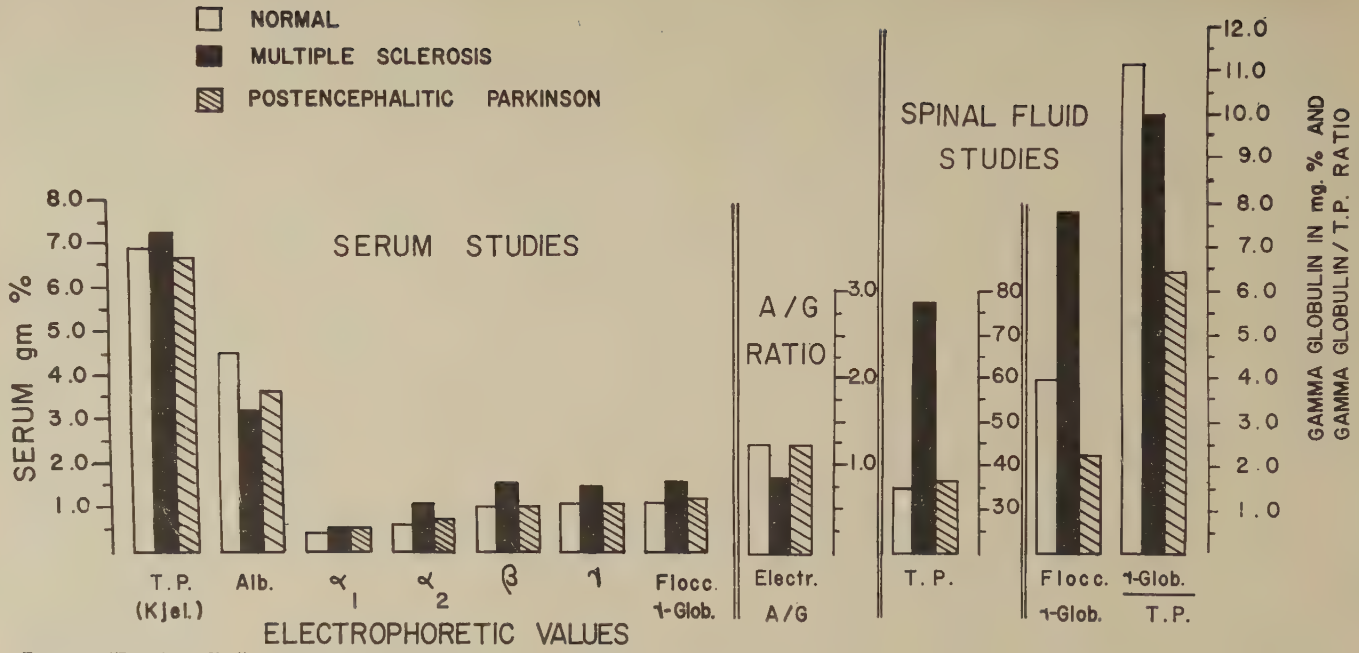

FIGURE 2 "Protein profiles" of protein fractions found in the blood serum and cerebrospinal fluid of a patient having multiple sclerosis (M) and of another patient having arteriosclerotic Parkinsonism (P) as compared with that of a normal individual (N).

The mean values obtained by using the protein flocculation-ninhydrin method checked with those obtained through the immunochemical technique over a wide range of concentrations. Moreover, the distribution of these 100 fluids followed closely the pattern obtained in a similar study of Kabat, *et al.*[28] using the immunochemical method.

(C) *Protein Profile of Serum and Cerebrospinal Fluid in Multiple Sclerosis.* The characteristic protein findings for serum and cerebrospinal fluid in a representative case of multiple sclerosis, as compared to the mean normal value for each component, are shown in FIGURE 2. This kind of pattern of the various protein fractions had been termed by us the "protein profile" characteristic for this disease. We believe that this combination of serum protein findings together with the cerebrospinal fluid values provide the clinician with an additional number of parameters upon which to base a diagnosis of multiple sclerosis. For example, it has been reported by several investigators[24, 25, 31] that a change in the cerebrospinal fluid protein fractions in most diseases, *e.g.*, gamma globulin, is usually associated with similar changes in the serum protein fractions. Kabat, *et al.*,[25, 28] however, have suggested that for certain neurological diseases, such as multiple sclerosis, the rise in the crebrospinal fluid gamma globulin may be owing in part to the formation of antibody proteins synthesized by the central nervous system Such a viewpoint would account for the level of the serum gamma globulin remaining normal or being slightly increased, as compared to the rather marked elevation of this component in the cerebrospinal fluid (FIGURE 2).

So far our studies have been concerned primarily with protein changes of carefully selected, clinically typical cases of multiple sclerosis. We have extended our investigation to a limited number of patients having a variety of other neurological disorders such as amyotrophic lateral sclerosis, hemiplegias, postencephalitic or arteriosclerotic Parkinsonism, *etc.* These patients showed "protein profiles" which were definitely different from those shown by cases of multiple sclerosis. A "protein profile" of a representative case of arteriosclerotic Parkinsonism is also demonstrated in FIGURE 2. The material studied so far, however, is insufficient to draw any definite conclusions as to how distinct the "protein profile" for multiple sclerosis is in compairson with other allied neurological disorders. Further investigations in this direction are now in progress, as are studies dealing with the elaboration of simple quantitative protein flocculation methods for protein fractions other than gamma globulin.

Summary and Conclusions

(1) The protein fractions in serum and cerebrospinal fluid of 23 carefully selected clinical cases of multiple sclerosis were studied.

(2) The serum proteins of these patients were determined quantitatively with the electrophoretic method. In 85 per cent of the cases there is a significantly decreased albumin and A/G ratio, significantly increased alpha-2 and beta globulin fractions, a slightly elevated (or normal) gamma globulin fraction, and a normal alpha-1 globulin fraction. The remaining 15 per cent of these cases showed most but not all of these changes.

(3) Simple qualitative serum protein flocculation reactions were run simultaneously with these electrophoretic studies. Of those tested the highest percentage (66 per cent) was given by the cephalin-cholesterol flocculation reaction reflecting changes in the electrophoretic albumin component. The next highest number of positive results (21 per cent) was given by the thymol turbidity reaction which reflects changes in the beta globulin fraction. The zinc sulfate turbidity reaction and the ammonium sulfate-sodium chloride turbidity reaction show only a small number of positive tests reflecting a normal or slightly increased serum gamma globulin value for the series of 23 multiple sclerosis cases.

(4) The quantitative protein flocculation-ninhydrin procedure for the determination of serum gamma globulins were also run for these 23 cases of multiple sclerosis. The values obtained by this method corresponded closely with the electrophoretic data. The total serum-gamma globulin values obtained with the protein flocculation-ninhydrin procedure were also elevated, reflecting an increase in the electrophoretic beta fraction.

(5) The protein flocculation-ninhydrin method used for serum gamma globulins was applied to the quantitative determination of the gamma globulin content of dialyzed cerebrospinal fluid.

(6) The method used for serum was modified by the use of a stable desoxycholic acid-cholesterol emulsion. This emulsion gives more highly reproducible results and extends the useful range of the method to the lower gamma globulin levels found in cerebrospinal fluid. This simple method was found to check with the immunochemical method within ±1 mg. per cent for 100 cerebrospinal fluids from randomly selected neurological cases over a wide range of gamma globulin values and recovers small amounts of added gamma globulins with an average error of ±5 per cent.

(7) In this series of 23 cases about 80 per cent showed elevated cerebrospinal fluid gamma globulin values or increased gamma globulin/total protein ratio values.

(8) It is believed that the combined study of serum and cerebrospinal fluid protein fractions results in a "protein profile" which appears to be of diagnostic value for multiple sclerosis, as compared to other neurological diseases, in the limited series of cases thus far studied.

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FURTHER STUDIES ON THE GAMMA GLOBULIN CONTENT OF CEREBROSPINAL FLUID IN MULTIPLE SCLEROSIS AND OTHER NEUROLOGICAL DISEASES*

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Introduction

It has been known for some time[1] that an increase in cerebrospinal fluid globulin occurs in multiple sclerosis. Only recently[2] has this elevation been attributed to the gamma globulin fraction. To provide a quantitative method of determining gamma globulin in small amounts of cerebrospinal fluid, Kabat, Glusman, and Knaub[3] have devised an immunochemical procedure. In principle, this method makes use of rabbit antisera which will specifically precipitate albumin or gamma globulin from cerebrospinal fluid. Each may then be assayed and its exact amount determined. Since the absolute value of gamma globulin will vary with the amount of total protein, results are reported as the proportion of gamma globulin to total protein, expressed as per cent. Initial reports [4, 5] using this method have shown that a significant number of patients having multiple sclerosis show an increase in cerebrospinal fluid gamma globulin in such amounts that the gamma globulin constitutes more than 13 per cent of the total protein. However, this elevation in cerebrospinal fluid gamma globulin is not specific for multiple sclerosis, as it occurs with equal or higher frequency in neurosyphilis and occasionally in other neurological disorders.

Since the initial reports, there has been an opportunity to study a larger series of multiple sclerosis patients with particular reference to the relationship of cerebrospinal fluid gamma globulin changes to the clinical variations in this disease. Type of onset, course, and duration, number of attacks and lesions, and degree of disability have been evaluated in this manner. In addition, the cerebrospinal fluids of a wider variety of neurological disorders than previously reported have been analyzed as to their gamma globulin content. The present report deals with the results of this study.

Case Material

The records of 681 patients admitted to the New York Neurological Institute in whom cerebrospinal fluid gamma globulin determinations were performed were reviewed. All patients were examined by many observers who concurred in the diagnoses. All doubtful and inadequately documented cases were excluded from this study. TABLE 1 shows the distribution of these cases. There were 244 cases in whom a definite diagnosis of multiple sclerosis was made. Though attempts were made to be as conservative as possible in making this diagnosis, some cases may well have been included in whom future definitive studies or pathological examination will not confirm the diagnosis of

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TABLE 1

DISTRIBUTION OF CASES WITH CEREBROSPINAL FLUID GAMMA GLOBULIN DETERMINATIONS

	No. of cases
Multiple sclerosis	244
Syphilis—central nervous system	35
Other neurological disorders	330
Undiagnosed disease—central nervous system	42
No disease—central nervous system	30
Total	681

multiple sclerosis, and others may have been excluded which may later prove to have this disease. A laboratory study such as this one assumes added significance when supported by pathological confirmation, but it is almost impossible to study a statistically significant number of patients having multiple sclerosis in this manner. In the 244 patients reported here only three have come to autopsy, all having elevated cerebrospinal fluid gamma globulin, and the diagnosis of multiple sclerosis has been confirmed. The 35 patients having syphilis of the central nervous system were of the usual varieties, and all were confirmed serologically. The group of 330 patients termed "other neurological disorders" comprises a heterogenous group of diseases of the nervous system, including tumors, infections, and vascular and degenerative disorders. Confirmation of the clinical diagnosis by a definitive laboratory procedure such as myelography, air studies, arteriography, or a tissue diagnosis, either through surgical specimens or autopsy, was obtained in 11 per cent of these cases. The rest conformed to well-defined clinical entities and, whenever any doubt existed, they were classified as undiagnosed diseases of the central nervous system. This latter group contained 42 patients among whom, as nearly as could be determined, there were no clinical grounds to suspect multiple sclerosis. There were 30 additional patients who had spinal fluid studies, but in whom no evidence of organic disease of the nervous system was found. The total of 681 cases did not include 50 patients whose clinical data was insufficient for proper evaluation.

TABLE 2

DISTRIBUTON OF CASES HAVING ELEVATED* CEREBROSPINAL FLUID GAMMA GLOBULIN

	No. of cases	No. of cases having elevated gamma globulin	Per cent cases having elevated gamma globulin
Multiple sclerosis	244	162	66.5
Syphilis—central nervous system	35	26	74
Other neurological disorders	330	23	7
Undiagnosed disease—central nervous system	42	2	5
No disease—central nervous system	30	2	7

* An elevated gamma globulin denotes cases in which over 13% of the total protein was gamma globulin by immunochemical assay.

Results

Table 2 shows the number of cases in each diagnostic group in which elevation of the spinal fluid gamma globulin was found. In the multiple sclerotic group, 162 cases or 66.5 per cent were found to have an elevation of the cerebrospinal fluid gamma globulin. This is somewhat lower than the 85 per cent reported by Kabat, Freedman, Murray, and Knaub.[5] Their cases, however, were primarily patients in a chronic disease hospital manifesting severe and disabling forms of multiple sclerosis and, as will be shown later, this particular factor may play a role in altering the cerebrospinal fluid gamma globulin. Of the 35 patients having neurosyphilis, 74 per cent showed elevation in cerebrospinal fluid gamma globulin. No relationship was evident between the degree of activity and/or antileutic treatment and the elevation in cerebrospinal fluid gamma globulin. There were 23 patients of the 330 termed "other neurological disorders," two cases in the "undiagnosed," and two in the "no disease" group of the central nervous system that showed elevated cerebrospinal fluid gamma globulin. These 27 cases comprise about 6 per cent of the total number of patients studied, and their diagnoses are detailed in table 3. The first eight

Table 3

Cases other than Multiple Sclerosis or Syphilis having Elevated Spinal Fluid Gamma Globulin

	No. of cases	Per cent gamma globulin
Periarteritis nodosa	3	19
		14
		14
Behcet's disease	1	29
Rheumatoid arthritis	1	14
Sarcoidoses	1	15
Leprosy	1	15
Alcoholic polyneuritis with cirrhosis	1	15
Meniere's syndrome	1	15
Trigeminal neuralgia	1	16
Bell's palsy	1	14
Tumors—central nervous system	3	
Primary: neurofibroma		19
Metastatic:		
Carcinoma lung		17
Site unknown		22
Syringomyelia	1	14
Heredito-degenerative disease of CNS	3	14
		20
		15
Cerebro-vascular disease	1	14
Osteoarthritis with cord compression	1	16
Platybasia	1	18
Cortical atrophy—unknown cause	1	22
Herniated nucleus pulposus	1	16
No central nervous system disease	2	15
Undiagnosed disease—central nervous system	2	16
		20
Total	27	

patients have systemic disease processes associated with an increase in serum gamma globulin, and their increase in cerebrospinal fluid gamma globulin may be accounted for on this basis.[2, 6, 9] The next three patients have symptom diagnoses with no apparent etiological agent. Whether some obscure etiological factor may be present which would account for the elevation in gamma globulin is of course unknown. At any rate, there were 15 similar cases having identical diagnoses with normal cerebrospinal fluid findings. The three tumor cases which follow were confirmed by histological study. In two of these cases,

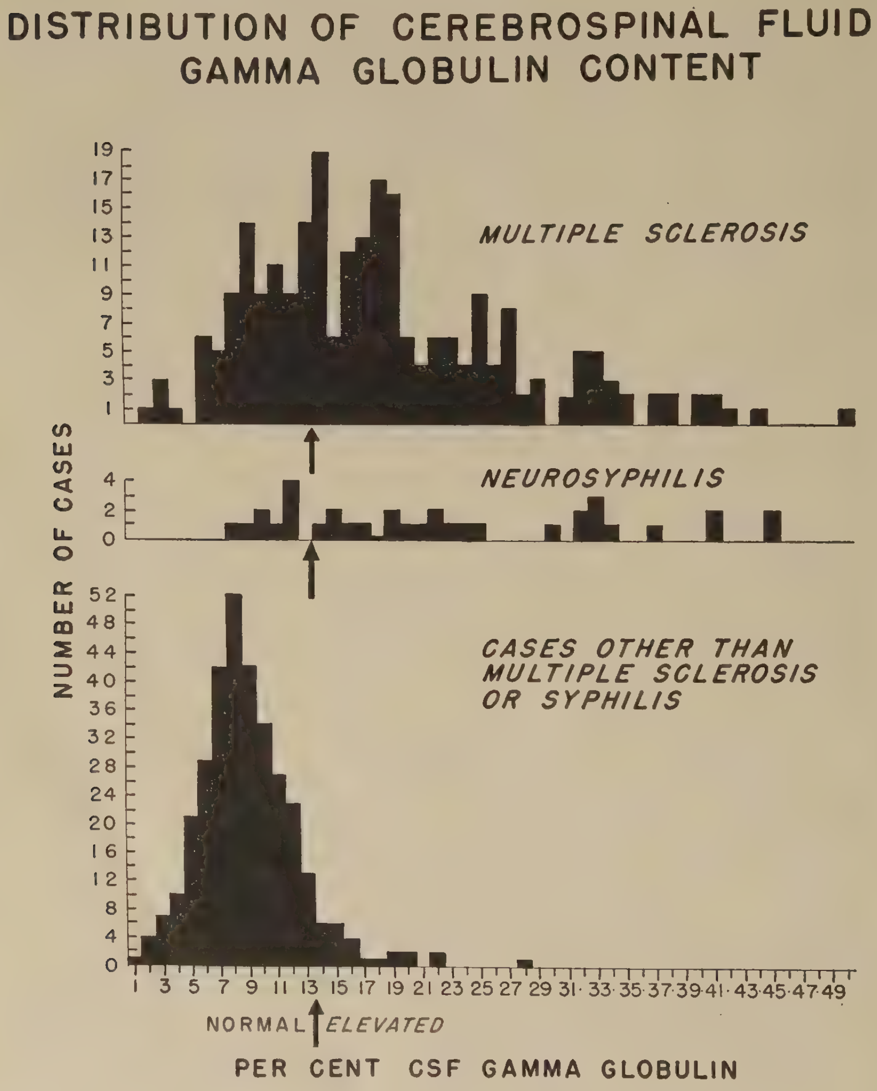

Figure 1

metastatic disease in other organs, particularly the liver, may have existed with alteration in blood and consequently cerebrospinal fluid gamma globulin. The rest, 11 in number, cover a wide variety of neurological disorders, and two cases had no disease of the central nervous system. There is no reason apparent for the elevation in cerebrospinal fluid gamma globulin in these cases. Though the number of such cases is low they emphasize the fact than an increase in cerebrospinal fluid gamma globulin is not specific for multiple sclerosis. When neurosyphilis is eliminated by serological testing, however, and increases resulting from hypergammaglobulinemia in the blood are taken into account, the incidence of nonmultiple sclerosis cases showing elevation of cerebrospinal fluid gamma globulin is relatively small. In the present series, it totals less than three per cent.

The distribution of gamma globulin levels among cases of multiple sclerosis, neurosyphilis, and other neurological disorders is compared in FIGURE 1. Multiple sclerosis and neurosyphilis behave similarly, over half the cases showing elevations above 20 per cent and, occasionally, cerebrospinal fluid gamma globulin constituting up to 45 per cent of the total protein. Abnormal gamma globulin levels in diseases other than multiple sclerosis and neurosyphilis are usually below 20 per cent, although in isolated cases values as high as 29 per cent have been found. Consequently, though the magnitude of the elevation of cerebrospinal fluid gamma globulin in a large group of patients having multiple sclerosis or neurosyphilis is greater than in other neurological disorders, as regards the individual patient, this criterion is of little value.

The multiple sclerosis cases were subjected to an extensive study with a view to elucidate any relationship of the clinical features of the disease to the alteration in cerebrospinal fluid gamma globulin.

The generally accepted type of onset (acute or chronic), and course (remitting or unremitting) was first evaluated. There were 53 patients in whom initial symptoms began acutely, and 130 patients showing insidious onset of the disease process. As shown in TABLE 4, the cerebrospinal fluid gamma globulin findings were similar in the acute and chronic groups, 75 per cent of the patients showing an elevation. Similar results are obtained when the cases are distributed as to the course of the disease. There were 112 patients in whom remissions occurred, and 74 in whom the disease ran a progressive unremitting course. In each instance, 75 per cent of the patients had elevated cerebrospinal fluid gamma globulin. Further evaluation was carried out by combining the type of onset with the clinical course without finding any added correlation.

Though it is extremely difficult to study the disease process in an individual patient over a prolonged period, a large series such as this affords the opportunity of observation of multiple sclerosis at various time intervals. In TABLE 5, the duration of the disease, from onset of first symptom to time of cerebrospinal fluid gamma globulin determination, by yearly intervals from one to over 30 years have been charted. No significant correlation between duration of multiple sclerosis and elevated cerebrospinal fluid gamma globulin was found.

As an index of activity of multiple sclerosis, the most recent symptom in relation to the time at which the cerebrospinal fluid was studied was recorded in

TABLE 4

RELATION OF TYPE OF ONSET AND COURSE OF MULTIPLE SCLEROSIS TO CEREBROSPINAL FLUID GAMMA GLOBULIN CONTENT

Type of onset	No. of cases	Per cent having normal CSF gamma globulin	Per cent having elevated CSF gamma globulin
Acute	53	24.5	75.5
Chronic	130	25.0	75.0
Type of course			
Remitting	112	25.0	75.0
Unremitting	74	24.3	75.7

TABLE 6. The data clearly show no correlation between these two factors. No differences in the incidence of elevated gamma globulin were noted in cases in which only one month or less had elapsed between onset of symptoms and gamma globulin determination, nor in cases in which no new symptoms had occurred for as long as two years prior to the gamma globulin determination.

Since Freedman and Merritt,[4] in their review of cerebrospinal fluid changes in multiple sclerosis, had reported that an elevated cell count was related to the time of an exacerbation of the disease process, a correlation between cerebrospinal fluid cell count and gamma globulin levels was carried out (TABLE 7). In 148 patients having a normal cell count, 101, or 70 per cent, were found to have elevated cerebrospinal fluid gamma globulin. In 63 patients having five cells or more, 54, or 85 per cent, showed elevated cerebrospinal fluid gamma globulin. It is also noted that, with increasing numbers of cells, the incidence of elevated cerebrospinal fluid gamma globulin increases so that all fluids having 20 or more cells showed an increased gamma globulin. From this development, it appears that increased gamma globulin is usually present at the time of an exacerbation, but is not indicative of it, since it occurs frequently during any phase of the disease.

There are obvious limitations in determining the number of attacks or lesions in patients having multiple sclerosis. Both attacks and lesions may occur

TABLE 5

DURATION OF MULTIPLE SCLEROSIS IN RELATION TO CEREBROSPINAL FLUID GAMMA GLOBULIN DETERMINATION

Duration (years)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Over 20
Total no. cases	67	24	24	21	15	9	12	7	8	10	3	3	3	2	4	—	2	2	—	6	5
Normal C S F gamma globulin	20	9	4	3	2	4	3	2	2	2	2	1	—	1	1	—	2	—	—	2	—
Elevated C S F gamma globulin	47	15	20	18	13	5	9	5	6	8	1	2	3	2	3	—	—	2	—	4	5
Per cent cases with elevated C F S gamma globulin	70	62	83	85	86	55	75	70	75	80	33	66	100	50	75	—	—	100	—	66	100

TABLE 6

RELATIONSHIP OF MOST RECENT SYMPTOMS TO CEERBROSPINAL FLUID GAMMA GLOBULIN

Time (months)	1	2	3	4	5	6	7	8	9	10	11	12	24	60	Over 120
Total no. cases	62	17	17	11	8	9	2	2	1	3	—	34	24	13	14
Normal C S F gamma globulin	16	4	4	3	2	2	1	—	1	—	—	14	6	2	4
Elevated C S F gamma globulin	46	13	13	8	6	7	1	2	—	3	—	20	18	11	10
Per cent cases showing elevated C S F gamma globulin	74	76	76	72	75	77	50	100	0	100	—	59	75	84	71

without detection unless the patient experiences new symptoms, or unless new signs are found on examination. Consequently, in determining the number of attacks, patients designated as having a single attack were those exhibiting one episode of neurological symptomatology in which no progressive neurological signs were found. Whenever more than one attack was indicated, subsequent episodes of new symptoms were confirmed by neurological examination. With respect to the number of lesions, the evaluation was based on those patients whose signs and symptoms implicated one system against those in whom signs and symptoms of multiple system involvement could be found.

There were 51 patients showing a single attack of multiple sclerosis, and of these patients, 53 per cent had a normal cerebrospinal fluid gamma globulin and 47 per cent had an elevated cerebrospinal fluid gamma globulin (TABLE 8). In the group having multiple attacks, there were 161 patients, of which 127, or 78.5 per cent, had elevated cerebrospinal fluid gamma globulin. In 60 patients having multiple attacks, an accurate recording of the number of episodes was found. Though both patients having five attacks had elevated gamma globulin, there was little difference between two, three, and four attacks.

In a similar comparison as to number of lesions (TABLE 9), there were 31 patients having single lesions in which 38.7 per cent had normal and 61.3 per cent had elevated cerebrospinal fluid gamma globulin findings. In the multiple lesion group of 158 patients, 23 per cent showed normal and 77 per cent showed elevated cerebrospinal fluid gamma globulin. A more striking difference is found in recording the number of lesions separately, in which patients having from 2 to 5 lesions, 85 per cent or more, showed an elevation in cerebrospinal fluid gamma globulin.

TABLE 7

COMPARISON OF CEREBROSPINAL FLUID CELL COUNT WITH GAMMA GLOBULIN CONTENT

Cells per c mm	No. of cases	C S F gamma globulin	
		Normal	Elevated
0–4	148	47	101
5–9	31	6	25
10–19	21	3	18
Over 20	11	0	11
Total	211	56	155

TABLE 8

RELATION OF NUMBER OF ATTACKS OF MULTIPLE SCLEROSIS TO CEREBROSPINAL FLUID GAMMA GLOBULIN

	Single attack		Multiple attacks	
	No. of cases	Per cent	No. of cases	Per cent
Normal C S F gamma globulin	27	53%	34	21.5%
Elevated C S F gamma globulin	24	47%	127	78.5%
Total	51	100%	161	100%

Number of attacks	1	2	3	4	5	More than 1. Exact number undetermined
Normal C S F gamma globulin	27	3	2	3	0	26
Elevated C S F gamma globulin	24	25	13	12	2	75
Total cases	51	28	15	15	2	101
Per cent elevated C S F gamma globulin	47%	89%	86%	80%	100%	74%

Similar results were obtained using a crude index of disability incurred from the disease. Patients were graded from 1 to 4 as to their degree of functional impairment. In grades 3 and 4, which included patients afflicted by disabling forms of the disease, so that they were bedridden or limited to a wheel chair, consistent elevation in cerebrospinal fluid gamma globulin were found.

In evaluating the sites of lesions, the 19 patients having single lesions but

TABLE 9

RELATION OF NUMBER OF LESIONS OF MULTIPLE SCLEROSIS TO CEREBROSPINAL FLUID GAMMA GLOBULIN

	No. of cases having single lesions		No. of cases having multiple lesions	
Normal C S F gamma globulin	12	38.7%	37	23%
Elevated C S F gamma globulin	19	61.3%	121	77%
Total	31		158	

Number of Lesions	1	2	3	4	5	More than 1. Exact number undetermined
Normal C S F gamma globulin	12	8	5	0	0	24
Elevated C S F gamma globulin	19	40	24	3	1	53
Total	31	48	29	3	1	77
Per cent elevated C S F gamma globulin	61%	83%	83%	100%	100%	68%

having elevated cerebrospinal fluid gamma globulin, were particularly studied. There was no evidence of any predilection for a particular site in these cases. They were almost equally distributed between spinal cord, brain stem, cerebellum, and cerebrum. They varied little from the cases having single lesions and having normal cerebrospinal fluid gamma globulin findings except that six patients having retrobulbarneuritis, thought by many to be the initial episode of multiple sclerosis, all had normal gamma globulin findings.

From these data, it may be stated that the individual patient having multiple sclerosis, who has experienced multiple attacks, shows multiple lesions, and has a marked degree of functional disability, shows an elevation in cerebrospinal fluid gamma globulin of more than 13 per cent. Though the elevated cerebrospinal fluid gamma globulin in such instances is merely confirmatory evidence of multiple sclerosis, the absence of such a finding makes the diagnosis less certain. The following cases illustrate this fact:

Case 1. A. L., a 50-year old-female, gave a 10-year history of repeated episodes of parasthesias in the upper and lower extremities and a two-year history of progressive unsteadiness in gait. Neurological examination showed horizontal nystagmus, spastic paraparesis with hyperactive reflexes, Babinskis and confirmatories, absent abdominal reflexes. There was no clear-cut sensory level, but diminution in pain and vibratory sensibility were present in both lower extremities. The patient was markedly disabled and unable to walk without support. Cerebrospinal fluid studies were all normal, showing a gamma globulin of 8 per cent. Pantopaque myelography showed no filling defect in the spinal subarachnoid space. It was felt that this patient was suffering from a spinal form of multiple sclerosis, and she was hospitalized at a chronic disease hospital. Two years later she was found to have a sensory level at C_5 accompanied by a corresponding muscle atrophy. At operation, an extra medullary cord tumor at C_4 was found and removed.

Case 2. N. H., a 40-year-old female, had a 12-year history of intermittent attacks of double vision, parasthesias, and unsteady gait. For the previous three years of her illness, her symptoms had been progressive, so that at the time of her admission she was bedridden. Neurological examination revealed nystagmus, slurred speech, ataxia in the upper limbs, marked spastic paraparesis accompanied by hyperactive reflexes, Babinskis and confirmatories, and a decrease in vibratory and position sense in both lower limbs. During a one-year period of observation, in which her neurological deficit was progressive, three cerebrospinal fluid gamma globulin determinations were 18, 20, and 18 per cent respectively. One year later, this patient came to autopsy with typical lesions of multiple sclerosis scattered throughout the central nervous system.

Both of these patients had intermittent neurological symptomatology accompanied by extensive resultant neurological deficit and disability. In the first case, it was felt that the normal cerebrospinal fluid gamma globulin was of little aid, and the diagnosis of multiple sclerosis was made by exclusion. In light of the present data, one would be more cautious of this diagnosis. In the second case, the elevated cerebrospinal fluid gamma globulin was confirmatory of the suspected disease process.

TABLE 10

AVERAGE CEREBROSPINAL FLUID GAMMA GLOBULIN FINDINGS IN 35 PATIENTS HAVING ADVANCED STAGES OF NEUROLOGICAL DISORDERS

Diagnosis	No. of cases	Per cent C S F gamma globulin	
		Average	Range
1. Amyotrophic lateral sclerosis	11	6	3–10
2. Syringomyelia and syringobulbia	10	8	5–14
3. Friedreichs ataxia	3	9	7–10
4. Poliomyelitis	6	8	7–10
5. Olivo-ponto-cerebellar degeneration	1	8	
6. Combined system disease with pernicious anemia	4	9	7–12

Multiple attacks, multiple lesions, and marked functional disability imply extensive damage to the central nervous system. This factor by itself may conceivably play a role in elevating cerebrospinal fluid gamma globulin. Diseases other than multiple sclerosis or neurosyphilis with extensive destruction in the central nervous system were therefore studied. In TABLE 10, the average cerebrospinal fluid gamma globulin findings in 35 cases of advanced stages of amyotrophic lateral sclerosis, Friedrichs ataxia, poliomyelitis, syringomyelia, olivo-posto-cerebellar degeneration, and combined system disease are tabulated. In each of these disease processes, cerebrospinal fluid gamma globulin findings are within the normal range. It would appear, therefore, that destruction of neuronal tissue alone does not necessarily cause alteration in cerebrospinal fluid gamma globulin content.

When possible, the cerebrospinal fluid gamma globulin changes were correlated with the routine colloidal gold curve, as done at the New York Neurological Institute. As indicated in TABLE 11, 207 patients afflicted by multiple sclerosis had both studies performed. In only 74, or 35.7 per cent, was some abnormality in the colloidal gold reaction found. This abnormality was primarily a first-zone change, as 64 of the 74 patients occur in this category. In the same 207 patients, 159 or 76.8 per cent showed an elevation in the cerebrospinal fluid gamma globulin. While only three cases having a colloidal gold abnormality failed to show an elevation in cerebrospinal fluid gamma globulin,

TABLE 11

RELATION OF CEREBROSPINAL FLUID COLLOIDAL GOLD REACTION WITH GAMMA GLOBULIN

Colloidal gold reaction	No. of cases	C S F gamma globulin content	
		Normal	Elevated
First zone curve	64	3	61
Second zone curve	9	0	9
Third zone curve	1	0	1
No abnormality	133	45	88

Total number of cases 207
Total abnormal colloidal reaction 74 (35.7%)
Total elevated gamma globulin 159 (76.8%)

88 cases showing normal colloidal gold exhibited elevation in cerebrospinal fluid gamma globulin. The greater reliability of cerebrospinal fluid gamma globulin findings and the routine colloidal gold reaction is obvious from these data. Though more refined techniques of the colloidal gold reaction, as outlined by Lange[7] and recently reported by Von Storch[8], show a higher incidence (83 per cent) in multiple sclerosis, they also show a high incidence (36 per cent) in nonmultiple sclerosis cases. When this later figure is compared with the cerebrospinal fluid gamma globulin incidence of 6 per cent in nonmultiple sclerosis patients, its further reliability is established.

Discussion

Though an increase in cerebrospinal fluid gamma globulin occurs frequently enough (66.5 per cent) in multiple sclerosis to be a useful aid in diagnoses, it is not pathognomonic of this disease. It occurs in neurosyphilis (74 per cent), in cases showing increased blood gamma globulin, and occasionally in other neurological disorders (6 per cent). Such an increase is, however, a more reliable test than the routine colloidal gold reaction, for when both are performed on the same cerebrospinal fluid sample in patients having multiple sclerosis, twice as many patients show elevations in gamma globulin as do abnormalities of the colloidal gold curve. Reports on the newer quantitative colloidal gold test show a higher incidence of correlation (83 per cent), but the frequency of false positive reaction (36 per cent) detracts from its value. Though no positive correlation with the type of onset, course, duration, or occurrence of new symptoms is found between multiple sclerosis and an elevated cerebrospinal fluid gamma globulin, such an elevation is an expression of the degree of severity of the disease process. As such, its highest incidence is in cases showing multiple attacks and multiple lesions. The mechanism by which an increase in cerebrospinal fluid gamma globulin occurs in multiple sclerosis is still unknown. The increase is not derived from the blood, as previous studies[2] have shown that the serum gamma globulin content is normal. Increased permeability of the blood brain barrier does not appear to be a factor, as discrepancies between blood and spinal fluid A/G ratios are found[2, 5] which cannot be accounted for on this basis. It would appear that the increased formation of cerebrospinal fluid gamma globulin in multiple sclerosis takes place within the central nervous system itself. Support for this thesis is found in the work of Katzenelbogen[6] and of Morgan[10], who have shown that, under certain conditions, antibodies can be found within the neuraxis in the absence of antibody in the serum. The present findings suggest further evidence for this viewpoint, since cases showing multiple attacks and multiple lesions might be expected to have increased production of gamma globulin, the elevation in this case being more readily detectable.

Summary

(1) The results of cerebrospinal fluid gamma globulin determinations in 681 patients have been presented.

(2) An elevation in cerebrospinal fluid gamma globulin is found in 66.5 per

cent of the patients having multiple sclerosis, 74 per cent of the patients having neurosyphilis and in 6 per cent of patients having other diseases of the central nervous system.

(3) The highest incidence of cerebrospinal fluid gamma globulin elevations occur in cases of multiple sclerosis who have had multiple attacks, multiple lesions, and marked functional disability.

(4) No relationship exists between the type of onset, course, duration, or occurrence of new symptoms in multiple sclerosis and the elevation in cerebrospinal fluid gamma globulin.

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Part III. Clinical Methods

A STUDY OF THE SHORT- AND LONG-TERM EFFECTS OF ADRENAL STEROIDS ON THE CLINICAL PATTERNS OF MULTIPLE SCLEROSIS*

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In recent years, the hyperadrenal state induced by the administration of the hormones cortisone and corticotropin‡ (ACTH) has been utilized in the therapy of many varied disease entities, and gradually the physiologic and pharmacologic aspects of these substances have been defined.[16, 17] In general, the following effects have been regarded as being responsible for observed changes in the symptoms and courses of the disorders treated: a suppression of inflammatory and other mesenchymal tissue and cellular responses, an interference with allergic reactions and other defense mechanisms, and the many chemical alterations related to the profound metabolic disturbance. In certain instances, the rationale for this therapy was not clear, but it was felt that one or another of these factors might influence a condition for which existing therapeutic agents are inadequate. This was primarily the basis of the present study of the effects of the adrenal steroid activity on the clinical patterns of multiple sclerosis. Also, there was the suggestion from the work on acute allergic encephalomyelitis that the inciting factors or conditions leading to the development of multiple sclerosis might possibly be related to abnormal immunologic mechanisms.[9, 11]

Materials and Methods

Forty-two patients having multiple sclerosis have been treated. There were 31 women and 11 men in the group, ranging in age from 19 to 54 years. Their symptoms, at the onset of observation, varied in duration from two weeks (as in an episode of optic neuritis) to 14 years. The total durations of illness varied from one to 14 years, the majority being between one and one-half and six years. The history of spontaneous oscillations of symptom intensity was noted carefully.

Short-term observations were made in 33 patients to whom corticotropin was administered for one or two 14-day courses. The hormone was given intramuscularly every 6 or 8 hours to a total dosage of 80 or 100 mgm. per day. A one-week period of saline placebo injections preceded and followed the corticotropin course. These patients were hospitalized, and the following laboratory studies were carried out in most instances: determinations of blood electrolytes (sodium, potassium, carbon dioxide combining power and chlorides), and sugar, total eosinophil counts (before and after the initial 25 mgm. dose of ACTH and

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during the following days), electroencephalograms, electromyograms, and cerebrospinal fluid analyses including measurements of the gamma globulin. Quantitative tests of muscle strength were attempted with a Newman myometer, but these were neither reliable nor consistent. Comparative motion pictures were evaluated in certain cases. Special attention was given to fluid balance, blood pressure, weight, and psychological status. Potassium and ammonium chlorides were administered to control potassium depletion and water retention in many patients. Criteria of improvement were based primarily on the objective features of the clinical neurological examination.

Ten of the above patients and an additional nine were given cortisone acetate orally in an average daily dosage of 100 mgm. for longer term periods of from three and a half to 27 months. The average duration of treatment was 13 months, four patients continuing for two years or more. These 19 cases were observed as outpatients, being examined at regular, frequent intervals. Selected laboratory examinations, as indicated above, were performed periodically. In certain instances, patients were hospitalized for tests of adrenal cortical activity and administration of ACTH. At the termination of the project, the cortisone dosage was decreased gradually, and the patients were admitted to the hospital for evaluation.

Results

Previous reports of this investigation, primarily concerned with the short-term effect, have been presented.[6, 7, 8]

All the patients developed, in varying degree, most of the signs and symptoms of the hyperadrenal state, or Cushing's Syndrome. The significant complications related to this condition will be discussed below.

Short-term effects. The basic symptom patterns of the patients were evaluated with regard to the following main groups: spastic-paretic, cerebellar, bladder, sensory, visual (acute and chronic loss), and ocular movement (TABLE 1). Twenty-one patients (64 per cent) showed either no changes or mild alterations in their over-all status. These effects were regarded as owing to a spontaneous oscillation or the psychological suggestion effect of the treatment situation.

TABLE 1

EFFECTS OF CORTICOTROPIN ON SPECIFIC SYMPTOM COMPLEXES IN THIRTY-THREE CASES OF MULTIPLE SCLEROSIS

Symptom complex	Total no. patients with syndrome	Improvement rating*				
		1−	0	1+	2+	3+
Spastic-paretic	28	0	5	10	12	1
Cerebellar	24	2	4	11	6	1
Bladder	21	0	2	6	9	4
Sensory	23	0	20	3	0	0
Visual						
Chronic	11	0	10	1	0	0
Acute	3	0	0	0	2	1
Ocular movement	23	0	19	3	1	0

* 1− = slightly worse; 0 = no change; 1+ = slight improvement; 2+ = moderate improvement; and 3+ pronounced improvement.

Table 2

Cerebrospinal Fluid Protein Changes During Corticotropin Administration in Twenty Patients Having Multiple Sclerosis

Case	Before corticotropin therapy		On last day of corticotropin therapy		General clinical improvement
	Total protein (mg./100 cc.)	Gamma globulin (%)	Total protein (mg./100 cc.)	Gamma globulin (%)	
2	60	24	55	26	Moderate
4	54	13	59	11	Slight
5	55	12	62	12	Slight
6	30	7	33	7	Slight
7	30	14	28	13	None
8	27	9	29	8	Slight
9	34	10	35	8	Slight
10	35	9	53	7	Moderate
11	113	12	86	8	Slight
12	48	10	33	9	None
13	63	24	75	22	None
16	70	10	62	10	None
20	55	10	50	9	Moderate
21	38	20	24	21	Slight
24	120	14	147	16	Slight
26	108	10	56	11	Marked
29	27	18	28	10	Moderate
30	48	10	57	10	Slight
31	64	12	117	9	Marked
32	53	12	45	12	None

In five of this otherwise unchanged group, however, bladder or rectal dysfunction improved significantly. In two patients, ataxia, particularly of the head and upper extremities, became worse during treatment.

Twelve patients (36 per cent) showed changes suggestive of significant improvement in certain symptom patterns. Those most favorably affected (TABLE 1) were the spastic-paretic, cerebellar or ataxic, bladder, and acute visual. The effect on spasticity was most pronounced, appearing usually within the first week. This relaxation of spasticity allowed a greater utilization of available motor strength. These changes occurred without any significant alteration in the status of the reflexes with the exception of an elimination of patellar or ankle clonus in three instances. Spasticity appeared to be most affected when it was secondary to spinal cord rather than cerebral lesion. The most significant reactions were observed in patients having signs of less than two to three years duration.

Twenty-one patients had bladder dysfunction characterized by frequency, urgency, retention, and incontinence. In 13 (60 per cent) of this group, corticotropin induced a moderate to marked relief of these symptoms within five days.

Eleven patients had central scotomas of at least six months' duration. In only one patient (having a small scotoma) did any improvement occur. Three patients had large acute progressive scotomas of two weeks' duration. In one case, the scotoma cleared within one to four days. The other two patients showed a moderate improvement which occurred more slowly. Placebo trials were not utilized in these instances because of the nature of the involvement. Oculomotor disturbances (nystagmus, diplopia) were present in 23 patients and, in only one, was a significant change noted, a severe third-degree nystagmus reverting to a minimal first degree type.

There were no significant alterations in sensory deficits, although minor fluctuations in intensity and levels of hypalgesia and diminished vibratory sensation were noted.

In most instances, all of these effects were transient, appearing only during the course of hormone administration and lasting seven to fourteen days afterward. In two cases, the duration of improvement of motor function was six months, without further treatment. During these short-term treatment periods, there were no exacerbations indicating the development of new lesions. After the administration of the hormone was discontinued, the course of the illness usually progressed as previously, but in at least three instances, this appeared to be much more rapid and severe, as observed during a six-month follow-up period.

In no patient did the placebo achieve the same effects as the corticotropin, particularly with regard to spasticity and bladder dysfunction.

It was observed that alterations in cerebrospinal fluid protein may accompany the corticotropin administration. These alterations were not paralleled by any significant changes in serum proteins. Complete cerebrospinal fluid analyses were performed prior to and usually on the last day of the second two-week course of corticotropin in a representative group of 20 patients (TABLE 2). Although in one instance (case 26), clinical improvement was accompanied by a decrease in the total protein, in general there was no consistent correlation with either total protein or gamma globulin content. Actually, in another patient (case 31), there was an increase in cerebrospinal fluid protein associated with clinical improvement.

Long-term effects. Cortisone acetate was administered orally to 19 patients in dosages averaging 100 mgm. per day for three and a half to 27 months. The status of three patients remained stationary. Two patients, after having shown only minor oscillations, developed signs and symptoms of new lesions in exacerbations. These symptoms involved the brain stem in both instances and were mild and short in duration with but slight residuals. One of these patients, a woman aged 26, had three such exacerbations during 23 months of cortisone therapy. Her previous three-year history of the illness was characterized by one or two exacerbations yearly, all relatively mild.

Improvements in motor disability (especially spasticity) and bladder dysfunction, as described above, with regard to the short-term corticotropin series, occurred initially in 14 patients. Since seven of these patients had shown this improvement during preliminary administration of corticotropin, this was a selected group. When cortisone was given initially, effects similar to those with corticotropin appeared within one to two weeks or not at all. The improvement in these two clinical patterns was maintained only in four patients to the termination of the cortisone administration (for 16, 17, 26, and 27 months).

Regression to the previous untreated status occurred gradually within two to twelve months in ten patients. An increase of cortisone dosage to 200 mgm. per day or the administration of corticotropin (long-acting preparation Acthar-gel), 100 mgm. daily for one to two weeks had no further influence on the symptoms or signs. The treatment was discontinued then, in four patients, but in the remaining six the hormone was administered again at the previous dosage. Within three to six months a progressive increase in existing symptoms (especially ataxia and weakness, but also spasticity) occurred requiring cessation of treatment. One patient met with accidental death after nine months of cortisone administration.

"Physiological" complications or side-effects of long-term cortisone administration. Most of the patients developed signs of Cushing's syndrome during this period of prolonged hyperadrenalism. The relatively benign changes and their incidence in this group were: specific obesity (70 per cent), hirsutism (55 per cent), ankle edema (50 per cent), intermittent muscular weakness (40 per cent), menstrual irregularity (34 per cent), plethoric appearance (30 per cent), mild emotional disturbances (25 per cent), acneform dermatitis (20 per cent), poor wound healing or infections (15 per cent), blood pressure elevation (5 per cent), and purpura or easy bruising (5 per cent). No patient developed signs or symptoms of diabetes. The following serious complications required withdrawal of the cortisone: an overt psychotic reaction with paranoid and depressive or hypomanic features in a delirioid setting (two cases), prepsychotic paranoid behavior (one case), perforation of a duodenal ulcer (one case), osteoporosis with a compression fracture of the third lumbar vertebra (one case).

About 40 per cent of the patients developed a mild to moderate intermittent muscular asthenia with occasional cramping, which was either generalized or confined to the lower extremities. There were no concomitant changes in the clinical status or laboratory tests (including serum electrolytes) which suggested the origin of this symptom. It was not altered significantly by the administration of large amounts of potassium salts except in a few suggestive instances.

Effects of cortisone withdrawal. The cortisone was withdrawn gradually in all instances except when one of the serious complications necessitated a relatively abrupt withdrawal. In general, there were no untoward reactions or significant symptoms of adrenal cortical insufficiency even after 27 months of cortisone administration. All the patients had normal blood electrolyte patterns, and only two had an eosinopenic response to corticotropin (Thorn test) indicative of adrenal cortical hypoactivity in that sphere. A few of the patients developed a transient depression and irritability that was probably reactive.

The follow-up period after this withdrawal has been only one month thus far in nine patients treated until recently, and three to twelve months in those ten patients from whom cortisone was withdrawn previously for the various reasons cited above. The course of the illness progressed as before in this group, accompanied perhaps with some acceleration in two patients. It is still too soon to evaluate the follow-up status of the former group. Our observations indicate, however, that seven of these patients are now either at their pretreatment level or are progressing with increased symptoms. Two patients, of the group of four displaying maintained improvement, still sustain this improvement but show a mild increase of motor disability. Bladder function is still adequate in these patients.

No signs of adrenocortical insufficiency were found in any of the patients prior to the adminstration of the hormones. All had normal eosinopenic responses to corticotropin (ACTH). Steroid excretion studies unfortunately could not be carried out in this present series.

It is noteworthy that consistent eosinophil depression was not present during the period of treatment with cortisone in all cases. Occasionally the total eosinophil count exceeded 150 per mm.^{3} when clinical signs of hyperadrenalism were quite manifest. Also, there was no correlation between the eosinophil level and any clinical effects of the hormones on the neurologic symptom patterns.

Discussion

The effects of the administration of corticotropin and cortisone and the induction of the hyperadrenal state in patients having multiple sclerosis may be evaluated from two aspects: that of secondarily changing the signs and symptoms of disordered function caused by lesions which are not basically altered, or that of true therapeutic efficacy in relation to the disease process.

The therapeutic effectiveness of any agent in this disorder can be regarded as significant only if it (1) induces lasting remissions and prevents relapses or exacerbations; (2) halts further progression; and (3) produces these responses in a valid series of cases correlated against the chance factor of spontaneous remission. In about one third of the present series of patients showing spasticity, corticotropin or cortisone produced an effect of relaxation, which was then maintained, in a much smaller number of patients, by continued administration of the hormones. Not all cases of spasticity responded equally, and some patients showed no change. This effect and the improvement in bladder dysfunction, however, were the only symptoms or signs of any significant response. In some patients, signs of cerebellar involvement improved moderately; in others the ataxia became worse during the hormone administration. It appeared that the best reactions occurred in cases having symptoms of less than two to three years' duration.

A number of cases of multiple sclerosis have been treated with corticotropin by Forsham, Thorn, and Alexander[3] and by Fog[2] with results generally similar to those reported above. Fog found that the positive clinical effect of the hormone was correlated directly with a marked excretion of 17-ketosteroids or other signs of adrenal cortical hyperactivity.

Acute retrobulbar neuritis, occurring as a symptom in the course of multiple sclerosis, or as an isolated phenomenon has been treated with these hormones by McLean[13] and by Gammon, Scheie, Ojers, Tyner, and King.[4] Improvement was reported in a number of patients, but in general the results in this condition may be regarded as equivocal because of its unpredictable spontaneous course.

Regression of symptoms, signs of the spread of old lesions, and new exacerbations occurred in this series in certain patients during the course of hormone administration. The occurrence of relapse, or a rapid acceleration of the progression of the disease following withdrawal of the hormones has been noted in several of our cases and also by Forsham, Thorn, and Alexander[3] and by Denny-Brown.[1] It would appear, therefore, that the hyperadrenal state does not act in therapeutic fashion on the lesions or on the basic disease process in multiple sclerosis.

The symptomatic effects then probably represent secondary phenomena of either suppression of the inflammatory reaction accompanying the fundamental neural lesion or they are more likely related to the chemical changes involved in the profound metabolic disturbance, especially with regard to tissue electrolytes. These effects might produce a diminution in neuromuscular excitability. The actual mechanism is obscure, and investigation of these factors is continuing.

There was no evidence of a basic adrenal cortical insufficiency in any of the patients in this series. In agreement with this finding are the results of a more detailed study of corticotropin tests in ten patients having multiple sclerosis made by Garcia-Reyes, Jenkins, Forsham, and Thorn.[5] These investigators also found no evidence that multiple sclerosis interfered with hypothalamus-anterior-pituitary-adrenal cortex activation.

Of related interest are several reports of the effect of corticotropin and cortisone on experimental allergic encephalomyelitis. Moyer, Jervis, Black, Koprowski, and Cox[14] noted that corticotropin was able to reduce the incidence of signs of encephalomyelitis, but total prevention of brain lesions was not accomplished. Kolb, Karlson, and Sayre[12] were able to reduce the incidence of paralysis and mortality in their animals with small doses of cortisone. Kabat, Wolf, and Bezer[10] showed that cortisone could prevent the development of this encephalomyelitis by suppressing the appearance of the granulomatous response at the site of inoculation of brain emulsion. Similar results were reported by Roizin.[15] This granuloma is regarded to be involved in the formation of the antibody to the inoculated brain tissue. Therefore, in these instances the prevention or alteration of severity of encephalomyelitis by the hormones is most probably owing to the change in the highly specific experimental conditions necessary for production of the disease rather than to any fundamental effect on the disease itself. The implications from these findings cannot be transferred to any conditions bearing upon human demyelinating disease.

Summary and Conclusions

Corticotropin and cortisone were administered for short and long periods to a group of patients having multiple sclerosis. Improvement in certain motor symptoms, especially spasticity, occurred occasionally, but not consistently. Signs of regression, spread of old lesions, and development of new lesions appeared in a few instances during treatment. The progression of the disease appeared to be accelerated in some cases following hormone withdrawal. No definite changes regarded as curative appeared in this series. It is therefore felt that these hormones are not suitable therapeutic agents for multiple sclerosis.

The serious complications and side-effects of a chronic induced hyperadrenal state occur in relatively high incidence (over 20 per cent) and represent an important contraindication to the consideration of using these hormones for only symptomatic effects, particularly since high doses are necessary.

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EFFECTS OF MUSCLE ADENYLIC ACID IN MULTIPLE SCLEROSIS*

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Preliminary observations made during a pilot study of the treatment of multiple sclerosis with muscle adenylic acid were reported several years ago.[1] This study has been continued for three and one half years and extended. It now covers a total of 367 patient-months of treatment in 26 patients. While the results are encouraging, they are still too fragmentary for definite conclusions to be drawn as to the value of this kind of therapy. Since the preliminary report was published, however, the doses have been increased and observations of the effects of overdosage have been recorded. A lowering of the blood plasma cholesterol was observed in some patients receiving large doses.

Muscle adenylic acid is adenosine 5 monophosphate (FIGURE 1), the phosphoric acid ester of adenylriboside through the fifth carbon atom of ribose. It is different both chemically and biologically from yeast adenylic acid in which the phosphate is esterified with the third ribose carbon. Although it has long been known to be extremely important in the biochemistry of the living cell,[2] only in the past few years have supplies of sufficient quantity and purity for therapeutic trial been available.

Little is known of the pharmacology of muscle adenylic acid. As in the case of other purine derivatives, a weak vasodilator action has been noted following its use.[3] Transient effects of muscle adenylic acid on the myocardium have been described[3] and it has been shown to suppress the cortical spike potentials produced in the cat by topical application of acetylcholine but not those produced by strychnine.[4]

In normal human adults, as little as 20 mgm. of muscle adenylic acid as the sodium salt (My B Den),† injected intramuscularly frequently, but not invariably, produced a large increase in the concentration of adenosine triphosphate and adenosine diphosphate within the blood cells. This increase was equivalent to many times the amount of adenosine monophosphate injected, and it occurred in spite of the fact that, *in vitro*, the muscle adenylic acid did not even penetrate into the cells.[5] These observations suggested the possibility that there might be some "catalytic" effect on the entire organism leading to the intracellular synthesis of adenosine triphosphate and thereby to improved functional activity of the cells.

Multiple sclerosis is a mysterious disease of unknown etiology. Its pathology, although in some ways characteristic, shares many features with what seem to be entirely different disease entities. The clinical course may be extremely varied and is, if anything, typically atypical. Neither the pathology nor the clinical course necessarily indicate that all patients properly diagnosed as having multiple sclerosis are suffering from the same disease process, although it seems probable that most of them are.

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* This work was partially supported by a grant from Ernst Bischoff Company, Ivoryton, Conn.

† The muscle adenylic acid preparations used in this study were supplied by Ernst Bischoff Company, Ivoryton, Conn.

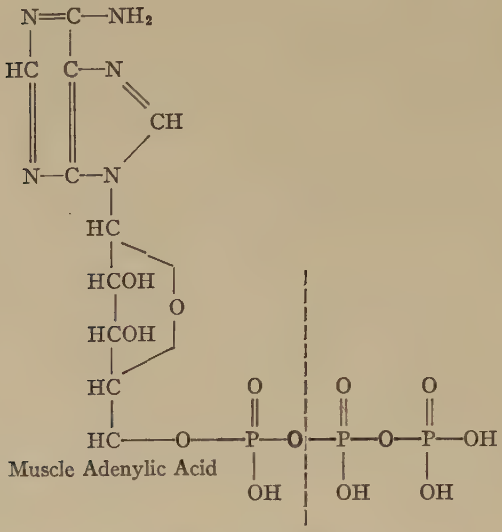

FIGURE 1. Molecular structure of adenosine triphosphate (the portion to the left of the dotted line represents muscle adenylic acid.)

One of the most disturbing aspects of the clinical problem of evaluating therapy of multiple sclerosis is the extreme difficulty and unreliability of prognosis. Apparently spontaneous remissions occur frequently. Conversely, when fibrous tissue has replaced axons in the development of the characteristic lesions in the central nervous system, no conceivable therapy can be expected to have any beneficial effect whatever on the lesions. Thus far we have no way of knowing at any particular time which symptoms are attributable to reversible lesions and which to irreversible ones. The adaptability of the human nervous system as a whole, and the profound effect of learning and of "state of mind" on the functional capacity of an individual having damaged fiber tracts also greatly affect both the symptoms and the signs of organic disease of the central nervous system.

While speculating about the possible significance of the apparently specific shift of intracellular nucleotide into high energy phosphate compounds, this investigator was faced with the clinical problem of what to do with a "hopeless case" of multiple sclerosis. This patient, a woman who had probably had the disease for about 25 years, had reached the stage where her family had been advised to arrange for permanent hospitalization. Her principal disabilities were fatigue, an unstable spastic gait, and urinary frequency, urgency, and occasional incontinence. She was receiving large amounts of vitamin B complex and vitamin C daily, intravenously and by mouth, and was barely able to continue her work as a school teacher. She was then advised to take a daily intramuscular injection of 20 mgm. of the sodium salt of adenosine 5 monophosphate dissolved in 1 ml. of sterile water. After the first few days she noted a marked improvement in her gait, her fatigue, and her bladder symptoms.

TABLE 1

COMPOSITION OF INTRAVENOUS VITAMIN SOLUTION—ONE DOSE

	mg.
Thiamine hydrochloride	110
Riboflavine	10
Pyridoxine hydrochloride	5
Calcium pantothenate	50
Nicotinamide	250
Ascorbic acid	500

At the time when the muscle adenylic acid injections were started, this patient was receiving frequent intravenous injections of a mixture of commercial vitamin preparations whose composition is shown in TABLE 1.* Thiamine and pyridoxine phosphates are coenzymes in many decarboxylation systems of the tissue cells. But riboflavin, pantothenic acid, and nicotinic acid amide form important compounds (FIGURE 2) with adenosine 5 monophosphate, which are necessary enzymes and coenzymes in the energy utilization of the cell as well as in the synthesis of substances essential to the structure and function of cells.[2] Diets deficient in these vitamins produce severe illnesses in experimental animals. There is a decrease in the concentration of the specific coenzymes and enzymes in which the specific vitamins occur,[6] and degenerative lesions of the central nervous system have been observed. In severe cases of human pellagra, which is usually attributable to a deficiency of both riboflavin and nicotinamide and often is accompanied by pantothenic acid deficiency, lesions of the long fiber tracts of the spinal cord and brain are often observed.[7]

Since it was suspected that the therapeutic actions, if any, of muscle adenylic acid in multiple sclerosis would be mediated by the intracellular synthesis of the adenine nucleotides (FIGURE 2), vitamins were given intravenously to all the treated patients in quantities in excess of their normal requirements as vitamins.

Dosage

Originally all patients were given a daily intramuscular injection of 20 mgm. of aqueous muscle adenylic acid daily and the vitamin mixture intravenously twice a week. In a few cases, where the 2 per cent aqueous solution was replaced by a 2 per cent solution in gelatin (My B Den Sustained Action), improvement previously noted seemed to be lost and patients were promptly returned to the original solution. The dosage of muscle adenylic acid has been gradually increased. This has been facilitated by the availability of 5 per cent and 10 per cent solutions. There was a general impression that the larger doses were more effective. Some patients showed improvement only when quite large doses were administered, and some relapsed when dosage was reduced because of side effects.

Recently, it has been considered advisable, whenever possible, to start intensive therapy in the hospital with muscle adenylic acid injections every six to eight hours and intravenous vitamins daily. Doses are gradually increased to the limits set by the tolerance of the individual patient. Three patients have received as much as 600 mgm. per 24 hours divided into four equal doses.

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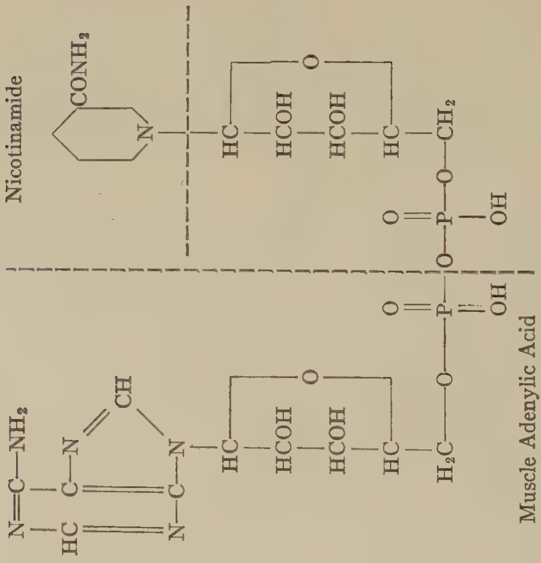
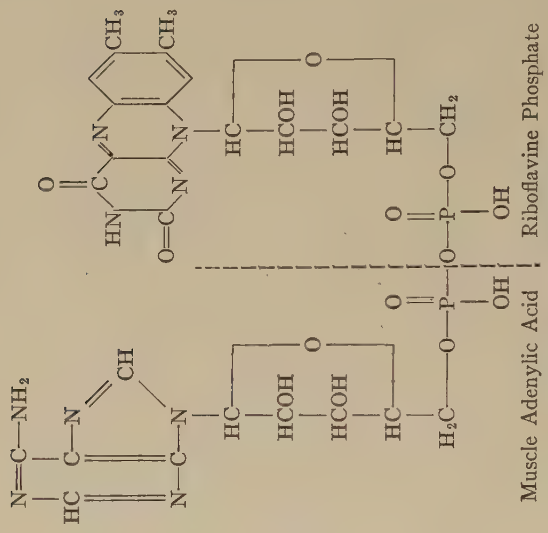
* Made up from SoluB (Upjohn) one vial; ascorbic acid 500 mgm.; and thiamine chloride, 100 mgm.



Coenzyme I



Flavine Adenine Dinucleotide

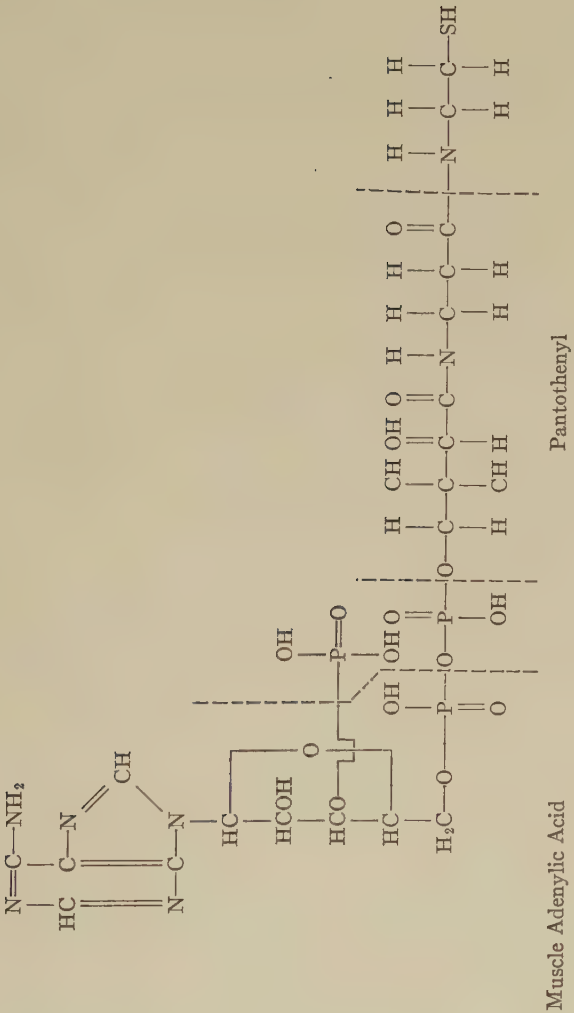


FIGURE 2. Molecular structure of important nucleotides containing muscle adenylic acid.

Upon discharge, each patient is given the same total amount of muscle adenylic acid per 24 hours in the form of two equal doses of a 48–49 per cent solution in gelatin.

Toxicity and Side Effects

Many of the patients noted a general sense of increased vigor and well-being, and slight wakefulness early in treatment, but since no placebo studies are available for comparison this effect is difficult to evaluate. The writer of this paper experienced a similar effect following a single intramuscular injection of muscle adenylic acid. The phenomenon lasted about eight hours and was equivalent to that experienced following a single oral dose of 10 mgm. of dexedrine sulphate.

Unpleasant side effects were rarely noted following doses smaller than 75 mgm. of aqueous muscle adenylic acid. With 75 mgm. or more, some patients complained of tightness in the chest, breathlessness, and "dizziness." These effects were experienced within a few minutes following the intramuscular injection and lasted up to 20 minutes. The patients rested quietly until the effects had worn off and were then apparently unharmed. Despite this discomfiture, most of them were willing to continue the treatment.

Three patients complained of what appeared to be a cumulative toxicity of the muscle adenylic acid. One, who had received 100 mgm. per day for several weeks, complained of a peculiar unsteadiness in walking and a tendency to fall to either side. This effect was not associated with the development of vertigo or ataxia and disappeared within 36 hours after discontinuing the injections. It was subsequently possible gradually to increase the dose to 75 mgm. twice a day without untoward effects. This patient had originally taken 20 mgm. per day and experienced increased improvement when she took the larger dose. Because she noticed substantial deterioration when the medication was stopped, she has adjusted her own dosage by trial and error to what she considers to be her limit of tolerance. For more than 14 months she has maintained herself on 75 mgm. twice a day without further toxicity.

The second patient was entirely bedridden when she was admitted to the hospital. She was started on daily intravenous vitamins and 20 mgm. of muscle adenylic acid three times a day. The latter was gradually increased to 100 mgm. four times a day over a period of three weeks. Two weeks after the start of therapy, when the dose was 100 mgm. three times a day, the comment was "slow general improvement, no objective changes." Five days after the dose was increased to 100 mgm. four times a day, the following note was made: "In the past three days there have been headaches 15 minutes after each injection of muscle adenylic acid, which lasted 15 minutes. Also, in the past 3 days, there has been definite improvement in bladder control and bowel movements have become spontaneous." The dose was reduced to 75 mgm. four times a day and, 19 days later, when the patient was discharged from the hospital, the following data were recorded: "Patient continues to have some side effects even on 75 mg. dose, but these are inconstant and variable in character—occasional headaches, dyspnea, etc. Clinically, the status is difficult to evaluate. She seems stronger, sits up in bed easily. Walking is somewhat better and appetite is good. Bladder and bowel function are much improved. On the other hand, objective neurological examination shows little change except for some increase in muscle strength." After leaving the hospital, the patient discontinued therapy because there was no further improvement, and has since become progressively worse.

The third patient experienced a cumulative toxicity similar to that of the first. She experienced no improvement under muscle adenylic acid therapy and, in fact, seemed to get worse. Although myelography had previously been reported as negative, it was now found to show compression of the cervical cord. Removal of a herniated intervertebral disc between C5 and C6 resulted in a marked improvement.

In another case, cumulative toxicity may have occurred. This patient started with 20 mgm. of muscle adenylic acid three times the first day, the next day increased to 40 mgm. three times a day, and three days later increased to 40 mgm. four times a day. After two days of the latter dose, she complained of the acute symptoms described above, following each injection. These symptoms continued despite reduction of the dose to 20 mgm. three times a day. When smaller doses were given there was no effect. Her symptoms, which had improved after the first few days of treatment, relapsed to their previous level.

Results of Therapy

The therapeutic results may be summarized very briefly (TABLE 2). Tabulation of the duration of treatment in the different categories of responses is not included, since, naturally, those patients who seemed to improve tended to continue therapy, while those who did not improve discontinued it after a relatively short time.

Among the 26 patients treated for a total of 367 patient months, there was only one relapse accompanied by the occurrence of new neurological signs or symptoms. This patient was taking the medications somewhat irregularly and the vitamins were given intramuscularly. He developed diplopia owing to paresis of a lateral rectus muscle, one-sided facial weakness, and paresthesia of the hand on the same side. He was given vasodilators by another physician while continuing the muscle adenylic acid therapy, and the new symptoms cleared almost completely in about four weeks.

TABLE 2
RESULTS OF MUSCLE ADENYLIC ACID THERAPY OF MULTIPLE SCLEROSIS

Response to therapy	Number of cases
No change	1
Slight but variable improvement not sustained	8
Slight but definite improvement	4
Moderate but definite and useful improvement	11
Complete and lasting relief of all symptoms and signs	2
Total	26

There was improvement in almost all signs and symptoms of multiple sclerosis in some patients at some time. Intention tremor, oculomotor paresis, nystagmus, abnormal reflexes, muscle spasm and paresis, disturbances of gait, sensory changes, bladder symptoms, all showed improvement in some cases. Bladder symptoms improved in every case in which they were present but all other disturbances failed to improve in at least one of the treated cases in which they were present. In some instances, improvement was not noted until weeks after the start of therapy. For this reason, six weeks has been selected as an appropriate trial period to determine whether a particular patient will benefit from this treatment. Cessation of therapy, in most cases where improvement seemed to have occurred, has been followed by a more or less rapid relapse to the pretreatment status. Two notable exceptions to this observation were the two earliest cases, who were also the two youngest patients and the two who had the most complete and lasting improvement. Since the earliest lesions have been found to be most responsive to other forms of therapy as well, further experience may show that such apparent therapeutic responses are in effect "spontaneous" remissions. Since we do not know the mechanism of "spontaneous" remissions, however, it seems necessary to attempt to determine whether one or more of the therapeutic agents used are capable of inducing such remissions and maintaining them.

Biochemical Observations

The original trial of muscle adenylic acid in the treatment of multiple sclerosis was inspired by the known importance of the substance in intracellular

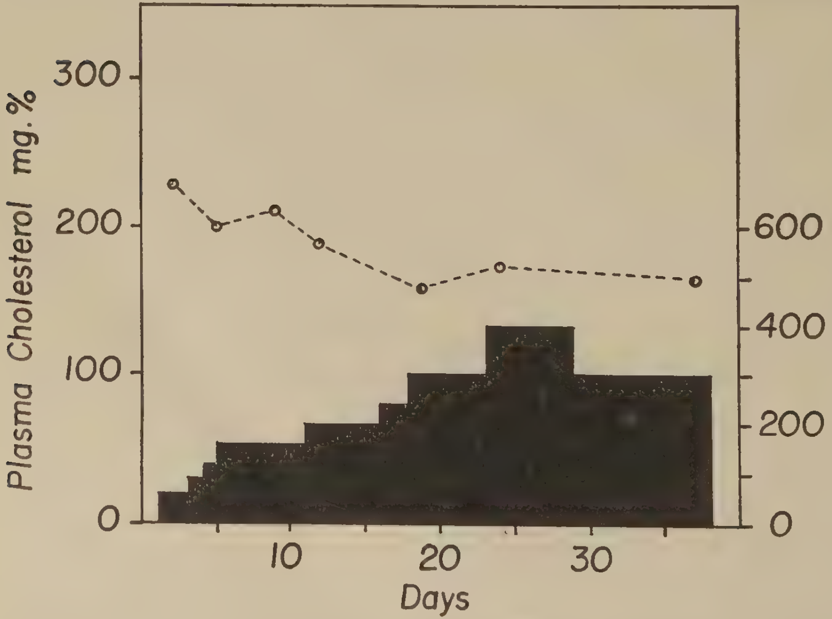


FIGURE 3. Plasma cholesterol concentration and muscle adenylic acid (A^5MP) dosage in a patient having multiple sclerosis.

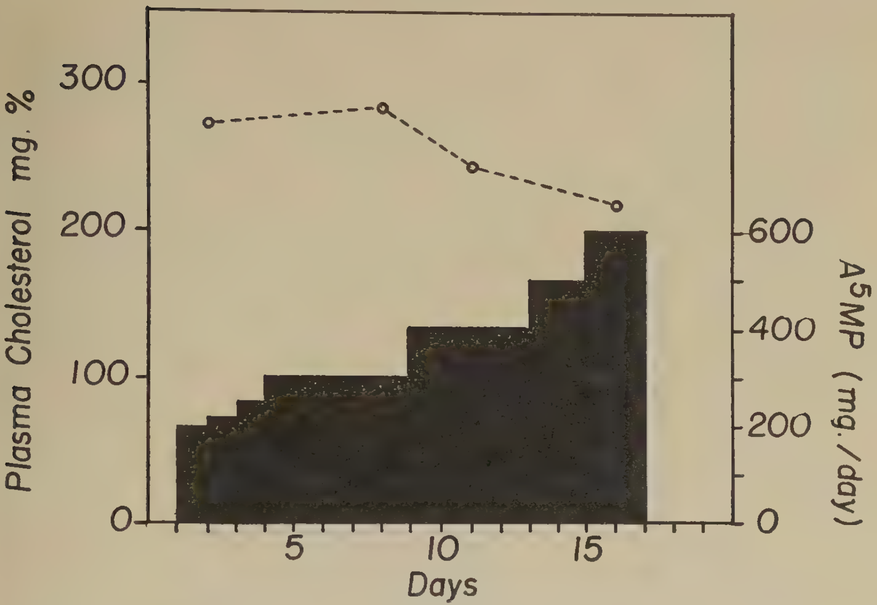


FIGURE 4. Plasma cholesterol concentration and muscle adenylic acid (A^5MP) dosage in a patient having multiple sclerosis.

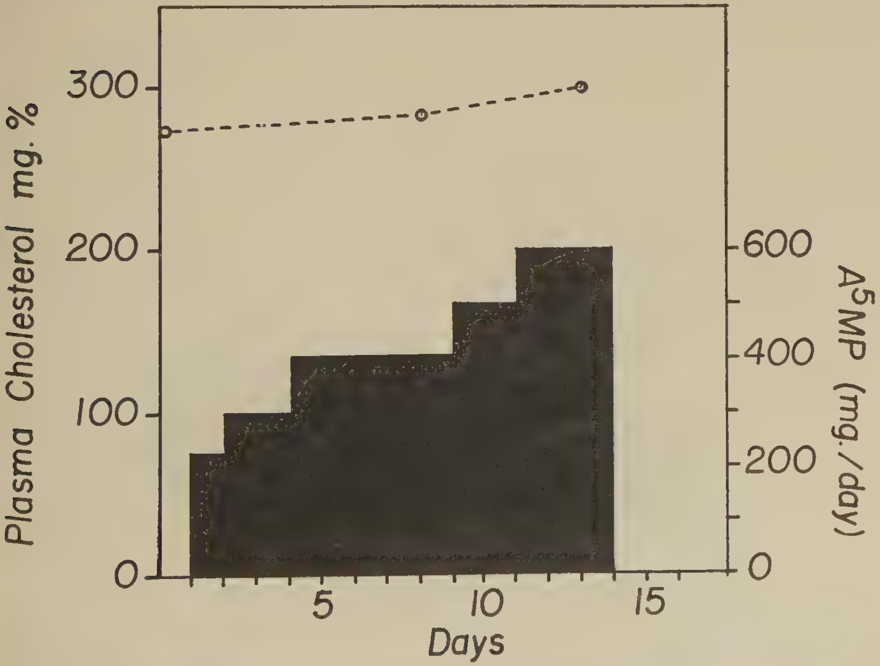


FIGURE 5. Plasma cholesterol concentration and muscle adenylic acid (A^5MP) dosage in a patient having multiple sclerosis.

chemistry and by the observed increase in high energy phosphate compounds in blood after injection of the drug into normal human subjects.[1, 2, 5] Thus far, there have been few opportunities for the study of adenosine triphosphate in the blood of multiple sclerosis patients. These few studies do not indicate either qualitative or quantitative differences from the behavior of normal individuals, but the number of observations is far too small for statistical evaluation.

A progressive decrease in blood plasma cholesterol was noted in some of the patients who received large doses of muscle adenylic acid. FIGURES 3 and 4 show the decrease in blood plasma cholesterol in two patients having multiple sclerosis under intensive treatment with muscle adenylic acid. Both were severe advanced cases who showed moderate but definite improvement while under therapy. FIGURE 5 shows a slight increase in blood plasma cholesterol in a patient who showed little or no improvement under treatment. FIGURE 6 shows a marked fall in blood plasma cholesterol in a patient afflicted by amyotrophic lateral sclerosis who experienced rather striking improvement while under therapy, and FIGURE 7 shows the decrease in blood plasma cholesterol found during treatment of a patient suffering from varicose veins and thrombophlebitis but having no neurological disease, and the subsequent rise in blood plasma cholesterol when muscle adenylic acid therapy was discontinued.

Just what relationship, if any, exists between the effect of muscle adenylic acid therapy on blood plasma cholesterol and the degeneration of the cholesterol-rich myelin sheaths of the long fiber tracts observed in patients having multiple sclerosis, remains to be determined. Further studies on the effect of muscle adenylic acid on blood plasma cholesterol in other diseases are now in progress.

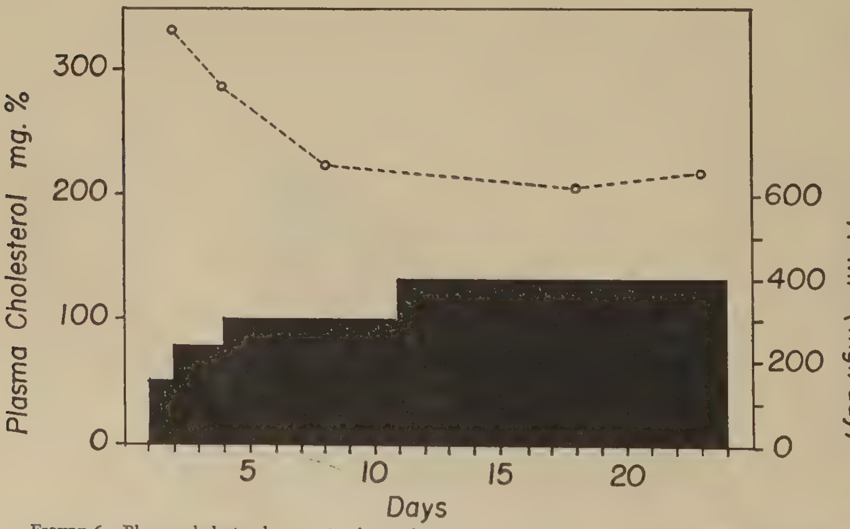


FIGURE 6. Plasma cholesterol concentration and muscle adenylic acid (A^5MP) in a patient having amyotrophic lateral sclerosis.

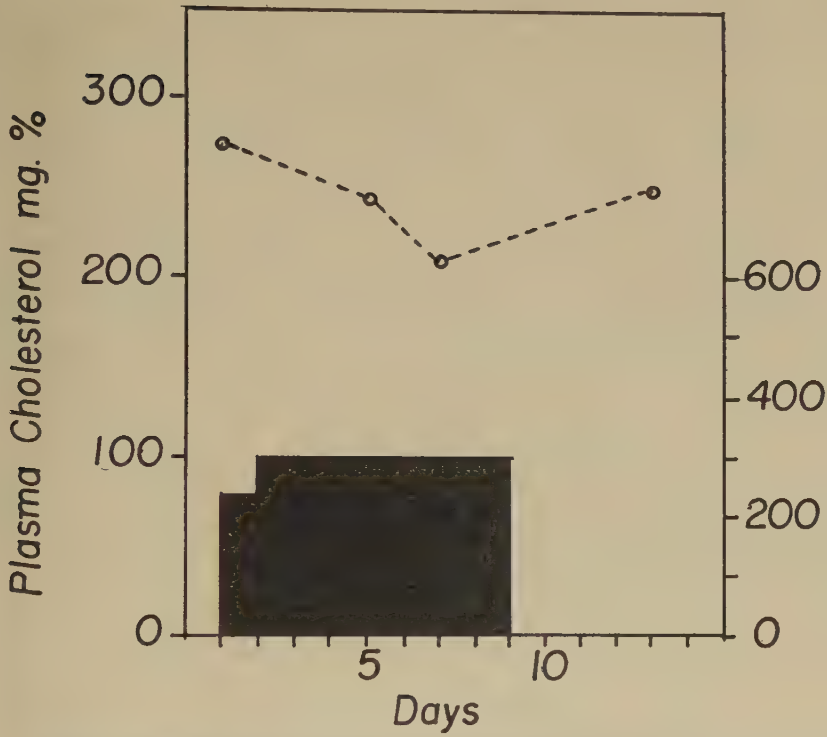


FIGURE 7. Plasma cholesterol concentration and muscle adenylic acid (A⁵MP) in a patient having varicose veins and no neurological disease.

Discussion

Muscle adenylic acid therapy for multiple sclerosis is based upon the assumption that one or more specific disturbances in intracellular metabolism play an important role in the pathogenesis of the disease. At this time, perhaps because of its current popularity among biochemists but also, at least in part, because of its established importance in the synthesis and breakdown of lipids, coenzyme A seems to be the most likely substance implicated. If this assumption is correct, there may be a very significant connection between the therapeutic responses of multiple sclerosis patients and the changes in blood plasma cholesterol which occur under intensive muscle adenylic acid therapy. The possible implications of these phenomena in multiple sclerosis, as well as in other diseases "of unknown etiology," are beyond the scope of this report, but further consideration would appear to be indicated.

Very little further can be said about the evaluation of therapeutic response. The infrequency of true relapse in patients under muscle adenylic acid therapy is perhaps the most definite and convincing therapeutic observation, although it, too, is far from conclusive. It would seem that large doses are relatively safe and probably desirable, but much remains to be done before an optimum therapeutic regimen can be devised and evaluated.

Summary

1. The progress of a three-and-one-half-year pilot study of the effects of therapy using muscle adenylic acid and water-soluble vitamins in 26 patients for 367 patient-months is reported.
2. Various doses of muscle adenylic acid were employed.
3. Side effects which were noted were not of a serious or permanent nature.
4. Results of therapy, although inconclusive, were encouraging.
5. Intensive therapy in some patients was accompanied by a definite and sustained decrease in blood plasma cholesterol.
6. Theoretical implications have been discussed.

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OPHTHALMOLOGICAL ASPECTS OF MULTIPLE SCLEROSIS

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Multiple sclerosis is a disease of the central nervous system which involves mostly the motor and sensory functions. It is most common in the first four decades of life. This crippling, depressing, and devastating disease strikes during the zenith of usefulness.

I was taught, as a medical student, that coarse intention tremors, nystagmus, and optic atrophy were diagnostic of multiple sclerosis. I have learned through the years that these are sure signs of the advanced stage of the disease. You will note that two of the triad of symptoms are elicited through the eye. Of the 12 pairs of cranial nerves, 50 per cent are directly connected with the eye. If we want to be liberal, the eighth nerve, through the vestibular apparatus and the tenth nerve, through cardiac inhibitory functions, are connected with the globe. So it is not too much to assume that the various aspects of multiple sclerosis may be revealed through ophthalmological study.

At the beginning, I should like to make it clear that my study has been *clinical* in nature, and has dealt with people who were suffering from multiple sclerosis.

During my 21 years at The New York Neurological Institute I have been privileged to see numerous cases of multiple sclerosis, but it was 11 or 12 years ago that I began to make recorded observations.

A patient, after complaining that his left eye was closing, was observed to have a spasm of the superior temporal arteriole. A confrontation field test was done during the episode, and an absolute scotoma was elicited corresponding to the position of the arteriole involved. This condition lasted for three or four minutes.

The visual complaints of my patients fall into five groups: (1) "There are shimmering, blurring spots before my eyes." (2) "Things dance before my eyes." (3) "I can see only a part of an object when I look at it" (transitory). (4) "I can't see to the side as well as I should." (5) "I can see an object, but it comes and goes."

I have found it both profitable and important to pay careful attention to a patient's visual complaint, for in many cases it gives one a clue to the type of field one may find. It has been my experience that visual acuity is usually reduced in active attacks of multiple sclerosis; occasionally, however, a patient in this condition will have 20/20 vision.

Fields of vision resulting from functional testing give four types: (1) a normal field with possibly moderate enlargement of the blind spots; (2) fields with central and paracentral scotomata; (3) fields with multiple isolated scotomata; and (4) a contracted field.

On external examination, many patients have diplopia with the red disc and light test. The lateral recti muscles are the most generally involved. Anisocoria (unequal pupils) is frequently present. I have discerned that the larger pupil is usually seen in the eye that has the most marked muscle involvement. The conjugate excursions from the primary position are nine in number and, in testing for diplopia, one should be meticulous in eliciting maximum conjugate excursions, or diplopia may be missed. A thorough understanding of the paired or yoke muscles involved in conjugate eye movements is basically necessary for the interpretation of diplopia.

I consider the fundi examination together with field study the most interesting if not the most important part in the examination of a multiple-sclerosis patient. I have observed the following in fundi of multiple-sclerosis patients: Advanced optic atrophy; temporal pallor of the discs; a generally narrowed retinal arteriolar tree; isolated spasm and narrowing of arterioles; complete spasm of one of the quadrant arterioles; hour-glass narrowing of both venules and arterioles; paravascular sheathing of venules; and circular small lesions about arterioles and venules. I have observed, in at least three cases, that these circular lesions have been most marked during a period of exacerbation and would tend to clear up with the remission. I have been unable to find that anyone else has made this observation. I have seen one case of multiple sclerosis where the vitreous was fairly flooded with opacities owing to uveitis.

Tremulous pulsations of arterioles in multiple-sclerosis cases, in my opinion, are worthy of careful consideration. I have not seen this vascular phenomenon in all cases but it is quite common and it has been observed in varying degrees in the same patient. Fuch's *Textbook of Ophthalmology*, translated by Duane, makes the following statement in section 408: "An arterial pulse is present under pathological conditions only." Ophthalmologists know that pulsating arterioles may be associated with glaucoma (increased intraocular tension). All multiple-sclerosis cases should have an intraocular tension taken prior to fundi study. We also know that the various blood dycrasias may present tremulous pulsating arterioles. Any type of anemia may be identified with this phenomenon. Since pulsating arterioles are accepted as being associated with either glaucoma or cardiovascular disease, it is not unreasonable to assume that the tremulous pulsations observed in multiple sclerosis may be significantly suggestive of a vascular process.

The type of thing that may precipitate an attack of visual disturbance in multiple sclerosis is no less interesting than it is unusual: passing from a dark room into the sunlight, eating a hot dish of food, taking a warm bath. Certainly eating and bathing would never be looked upon as forced drudgery, to say the least, and yet I have observed changes in the retinal arterioles as a result of both, and functional testing evidenced scotomata which were not there previous to the precipitated visual complaints. The thing that determines the color of an arteriole is the amount of blood it contains. An arteriole partially depleted of blood becomes light pink instead of a deeper red. An arteriole depleted of blood entirely becomes a white silvery streak in appearance. Observations of fundi in these cases revealed an increased redness of the arterioles following intramuscular administration of a vasodilator.

Probably the most striking observation in my clinical efforts is the effect vasodilators have on visual fields. In three of the four types of fields I have previously mentioned, intramuscular administration of a vasodilator gave an increase of the generally contracted field a minimum expansion of ten degrees; a diminished central and paracentral scotoma; and a diminished number of multiple scotomata. I have used as controls in these cases retinitis pigmentosa and disseminated chorio retinitis having an unknown etiology. In the controls, the fields remained unchanged following the intramuscular administration of a vasodilator, and I could observe no objective changes in the retinal vessels.

In conclusion, I wish to say, as requested by Doctor Wainerdi, that I have presented a skeleton outline only of the clinical work I have attempted. I have purposely avoided the humdrum of literature review, detail of technique, and multitudinous ramification of observations in my work and others. This discussion, I hope, will have as much appeal to the public as to the medical profession. Awakened to the seriousness of this disease, united in effort, willing to pool our efforts by increasing laboratory and clinical research, I am convinced that we can at least control this crippling, depressing, loathsome disease which this minute is casting shadows of darkness and gloom into tens of thousands of otherwise happy and useful lives.

MINNESOTA TEST AS A GUIDE TO THERAPY IN MULTIPLE SCLEROSIS

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Like all chronic diseases, multiple sclerosis produces anxiety in the patient. The way in which the patient deals with the anxiety is determined not only by the way in which the patient's adaptive processes were organized prior to the inception of the disease, but is dependent also upon the way in which the patient's family and friends may be drawn into the situation. The traumatic effect of facing a life of increasing helplessness, often of dependence upon those members of the family who were previously dominated by the patient and therefore might retaliate, sets up a chain of revisions of both conscious and unconscious aggressive drives which we believe are more often reflected in the physical symptomatology of the disease than is usually considered. A woman of 33 stated, "When the doctor told me I had multiple sclerosis I couldn't move for days. . . .I was accustomed to making the decisions in my family."

Hostility toward physicians who have failed them after making definite or indefinite promises as well as toward physicians who refuse to treat them also complicates the evaluation of the therapy. It becomes apparent to us that certain of the remissions and exacerbations occurring during electrophoretic histamine therapy could not be easily accounted for either by the therapy or by organic changes in the pathological processes.

A 40-year-old woman, formerly a ballet dancer, became almost completely paralyzed in both lower extremities in the course of therapy. This sudden change occurred after she had left the office of another physician who told her that our method of treatment would harm her. She became helpless on the street after leaving his office. It became evident as the course of the exacerbation was observed that there was probably no new pathology except, perhaps, in the attitude of her other advisor. Another woman, 26 years of age, married, complained of new muscular weaknesses which were soon resolved by the discovery that she did not wish to go away to the country with her mother-in-law. Similarly significant was the extraordinarily rapid improvement in a married woman of 30 after she had received small doses of histamine by iontophoresis from us, an improvement confirmed by her husband, who said "We went shopping and she walked me off my feet." These and other experiences have made it seem imperative to us that better psychological evaluation of patients must be obtained if the significance of any therapeutic procedure is to be determined.

The concept that patients having multiple sclerosis are euphoric has been current in the medical evaluation of this disease. In the rather brief psychiatric contact we have had with more than 100 patients belonging to this group in the past five years, however, the impression has developed that the categorization of personality structure of this illness by any single term is misleading. In previous publications, we have shown that there is a basic validity in the Minnesota Personality Inventory. This validity is based upon the fact that the consistent responses of patients after taking alcohol gave the same shaped curve as did the responses of the patients before taking alcohol. The Minnesota Test has served us as a rapid and safe psychological exploratory device in routine office practice. For this reason we have found it desirable to use the test as a guide in the therapy of multiple sclerosis by psychosomatic therapy.

Eleven patients studied consecutively but regrouped here are illustrated in CHARTS 1 to 11. CHARTS 1 to 8 are the Profiles in which therapy for a mental depression was suggested by the results of the Minnesota Test. In CHARTS 1, 2, and 3 the D score is the highest point and above 70. In CHARTS 5, 6, and 8 there are high values of the D score. CHART 8 depicts the Profile of a patient who had been bedridden for years. This patient improved to a surprising extent when her depressed state was recognized and treated. Even if the D score is comparatively low, as in the case of CHART 7, it is worthwhile to explore the possibility of the presence of a more serious depressed state than that indicated by the Profile Chart. Patient T. O. R. illustrated in CHART 9 has an M_a score above 70. We have pointed out previously, in regard to a group of personnel connected with the Chemical Warfare Service, that if the M_a score was relatively high compared to the other points it was significant of overactivity. This deduction was true of patient T. O. R., an alteration in whose condition may lead to a serious depression over the loss of much activity. The patients in CHARTS 9 and 10 were obviously seriously disturbed and were not amenable to the type of brief psychotherapy employed in the eight preceding patients. It is of interest to note that H. A. R. D. (CHART 9) was relieved by hydroelectric therapy administered by another physician through the vagina, but did not respond favorably to histamine administered by electrophoresis through the skin.

The cases of three patients already cited in the charts may be described in greater detail as follows:

CHART 1. D. O. L. is an example of a patient in whom the depressed state was readily determined by the Minnesota Test. She was a 36-year-old unmarried woman who had had multiple sclerosis for five years. At first she appeared to be tranquil and happy. The Minnesota Test, however, revealed that the one high point on her score was the D score. Her worst symptom was difficulty in walking. She had been receiving vitamin and other types of therapy as well as osteopathic therapy. On the basis of the clinical impression confirmed by the Minnesota Test, she was placed on d-amphetamine sulfate, 5 mgm. before breakfast and lunch. In addition, she was given tubocurarine and histamine by electrophoresis, and was placed on home therapy. The patient telephoned after one week of home therapy that she felt very well, was able to work around the house, and was able to do more than she had been able to do in years. To quote the patient, who sensed that it was the amphetamine that was effective, "I wanted to give my sister one of those wonderful pills, too."

CHART 3. S. M. I. was a young woman of 22 who had had the symptoms of multiple sclerosis for more than two years. She had had to give up secretarial work and now remained at home. Outwardly she seemed happy. She was living with her parents but she "did not like to be dependent upon anyone."

On her ninth visit to the office for histamine by electrophoresis, she produced an eight-page record of her life which she had written at home. She then became more relaxed and talked freely of her childhood. As a young girl she often daydreamed, "If my parents died or I were ill people would be sorry for me." The patient had improved with tubocurarine and histamine iontophoresis, but in view of the high value of the D score she was placed on d-amphetamine sulfate, 5 mgm. twice daily. This treatment resulted in further improvement, but because she exhibited slight jitters the amphetamine was replaced by a mixture

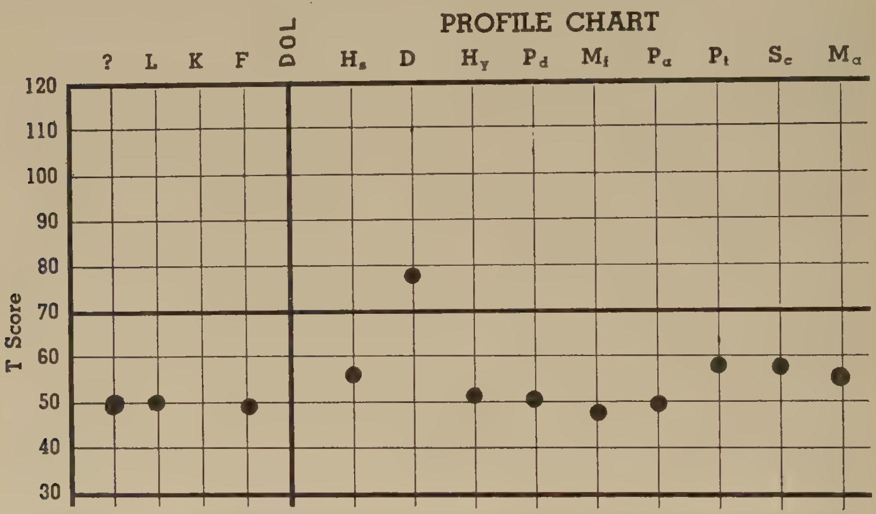

CHART 1. D. O. L., female, unmarried, age 36, duration of illness five years. Responded to both d-amphetamine sulfate and to a mixture of desoxyephedrine and acetyl carbromal.

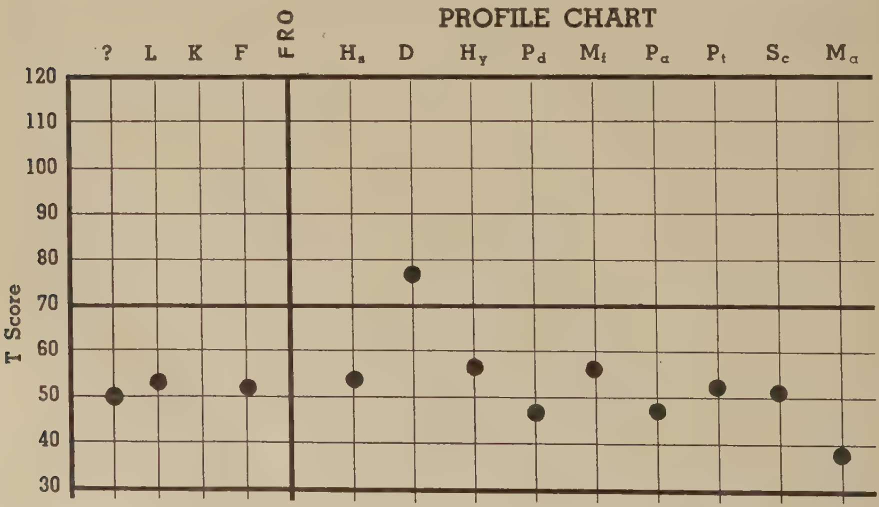

CHART 2. F. R. O., female, married, age 43, duration of illness 12 years. Responded to d-amphetamine sulfate.

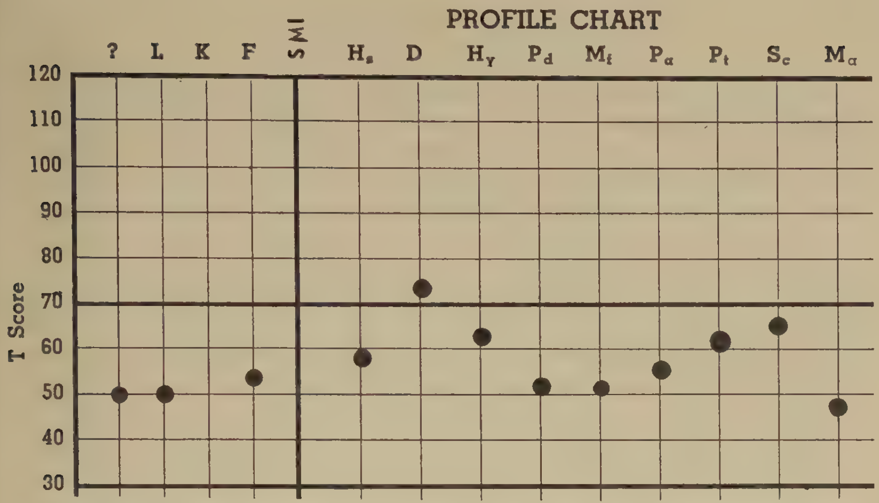

Chart 3. S. M. I., female, unmarried, age 22, duration of illness 2 years. Responded to both d-amphetamine sulfate and to a mixture of desoxyephedrine and acetyl C abromal. Able to return to work.

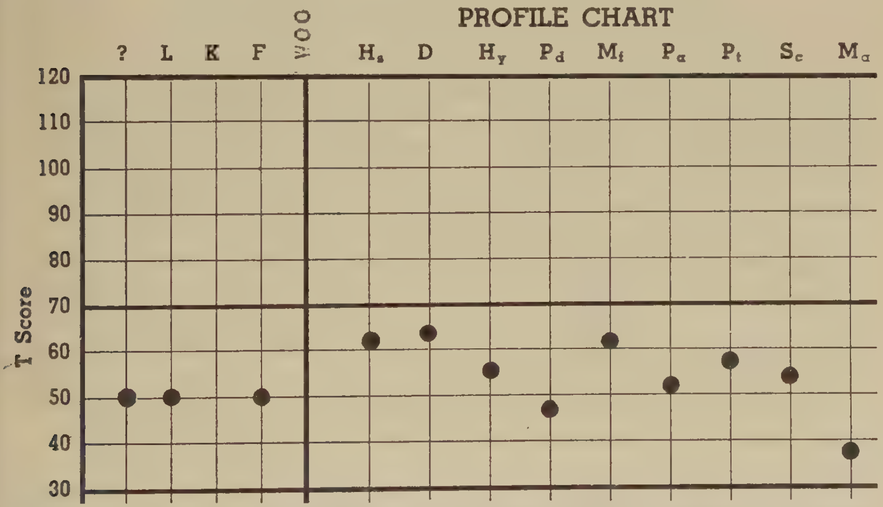

Chart 4. W. O. O., female, married, age 33, duration of illness one year. Responded to d-amphetamine sulfate. Able to return to work fulltime, able to take care of own home.

of desoxyephedrine and acetyl carbromal. This mixture* seemed to be helpful in overcoming the patient's depression. The Minnesota Test of this case led us to emphasize treatment of the patient's depression in spite of her outward gaiety. Mood-elevating drugs were accordingly used as well as brief psychotherapy. After several months of therapy, the patient was working at her former position five days weekly from 9:00 A. M. to 1:00 P. M.

Chart 7. F. A. R. was a woman of 43 who was only slightly disabled by

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* Kindly supplied by Schenley Laboratories, Inc.

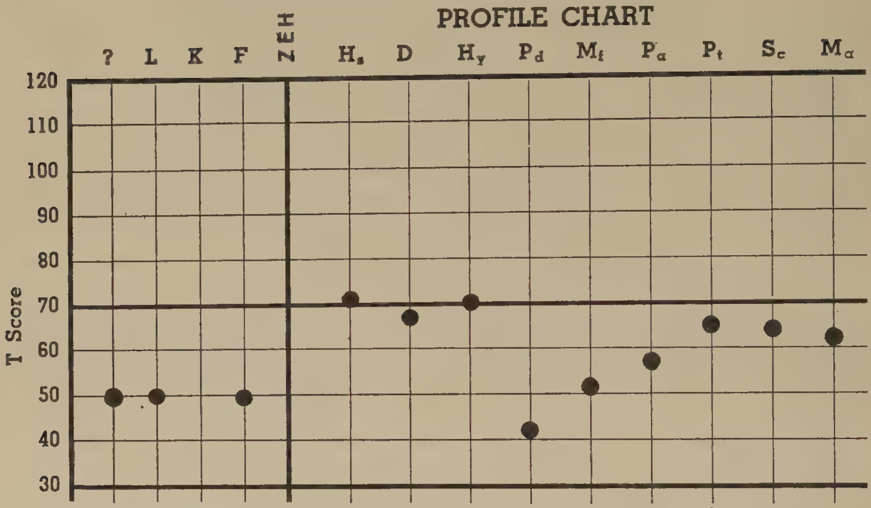

CHART 5. Z. E. H., female, married, age 28, duration of illness 3 years. Fair response to d-amphetamine sulfate.

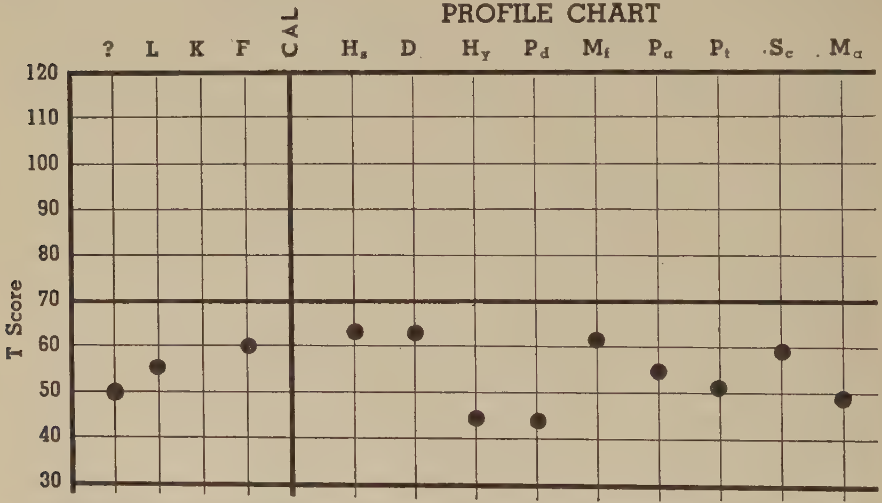

CHART 6. C. A. L., female, married, age 29, duration of illness 5 years. Required wheel chair, poor response to all forms of therapy.

multiple sclerosis, but she felt that she was much more comfortable when she used a cane. Nevertheless, she denied to herself and others that she was ill. Indeed, her denial led her to state, "I have no emotions, so to speak, or rather no emotional dependency on anyone." In later interviews, she did see the relationship of herself to her family. At first, histamine by electrophoresis was prescribed, but on further discussion and study of this patient, either d-amphetamine sulfate or a mixture of desoxyephedrine and acetyl carbromal seemed to produce a change in mood which was advantageous. In this case, the Minnesota Test did not give sufficient pertinent information.

We have found that the patient afflicted by multiple sclerosis, on becoming aware of the possibility of a future of progressive dependency, helplessness, loss of sphincter control, and increasing difficulty in communication, often undergoes a rather sudden change in adaptive technique. The patient, for example, might have to give up suddenly a position of dominance and substitute for it a

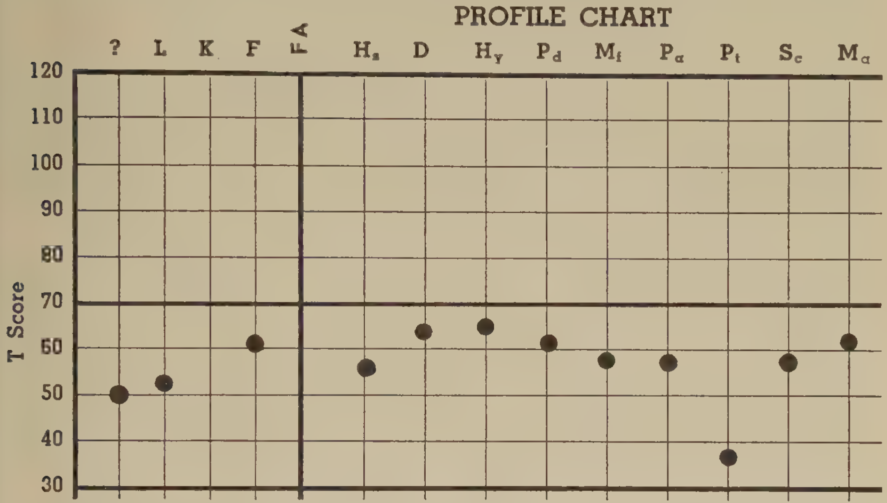

Chart 7. F. A., female, married, age 43. Fair response to acetyl carbromal and sedamyl, also fair response to d-amphetamine sulfate.

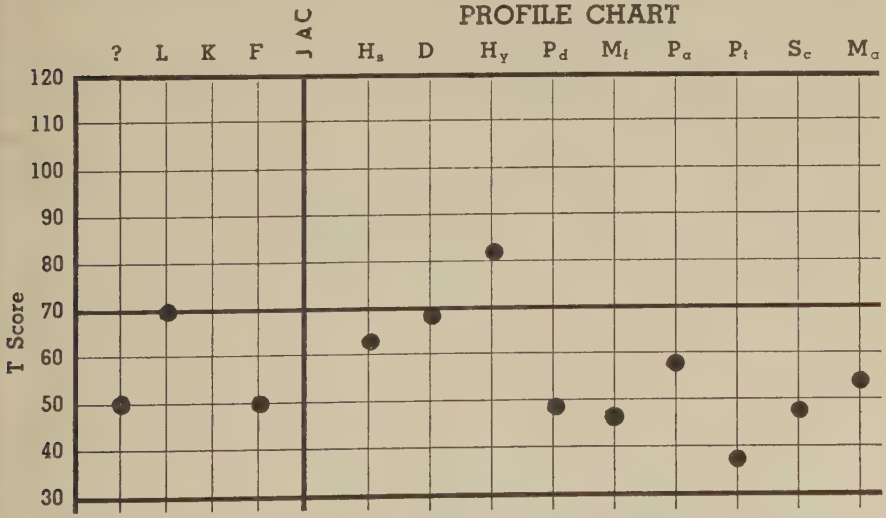

Chart 8. J. A. C., female, unmarried, age 35, ill many years, completely bedridden. Fair response to d-amphetamine sulfate.

passive role in which mature aggressive feelings rarely may be expressed. Often there is substituted a type of dependency where only infantile forms of dominating drives dare be shown. A sudden and almost automatic deprivation of the freedom to express normally hostile feelings toward the family has nearly always resulted, in our short series of cases, in an inner feeling of depression on the part of the patient. This hidden depressed feeling has been outwardly expressed, in some of the most helpless patients, by euphoric behavior and unrealistic attitudes designed to influence the family, the attendants, and the physician. The depression motivating the newly imposed adaptive process is

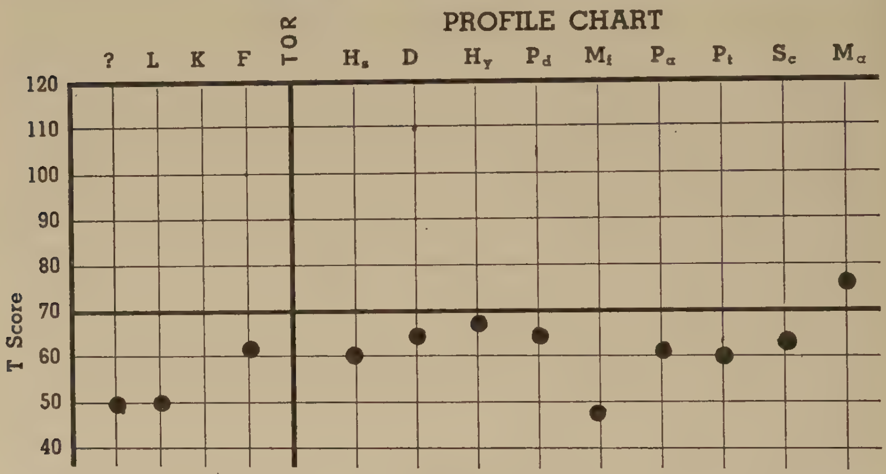

CHART 9. T. O. R., female, married, age 32, duration of illness 5 years. Patient hypomanic in behavior.

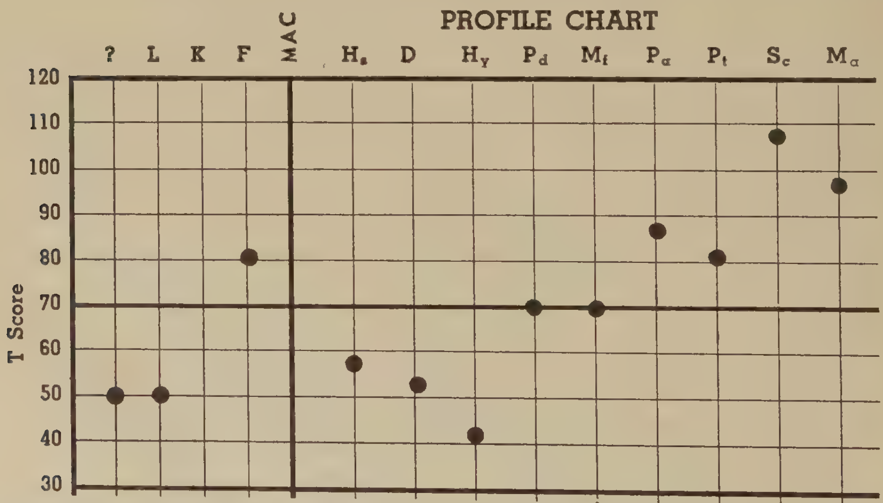

CHART 10. M. A. C., female, married, age 55, diagnosis amyotrophic lateral sclerosis, duration 2 years, patient extremely apprehensive, aided by amytal at night. Clinically extremely depressed.

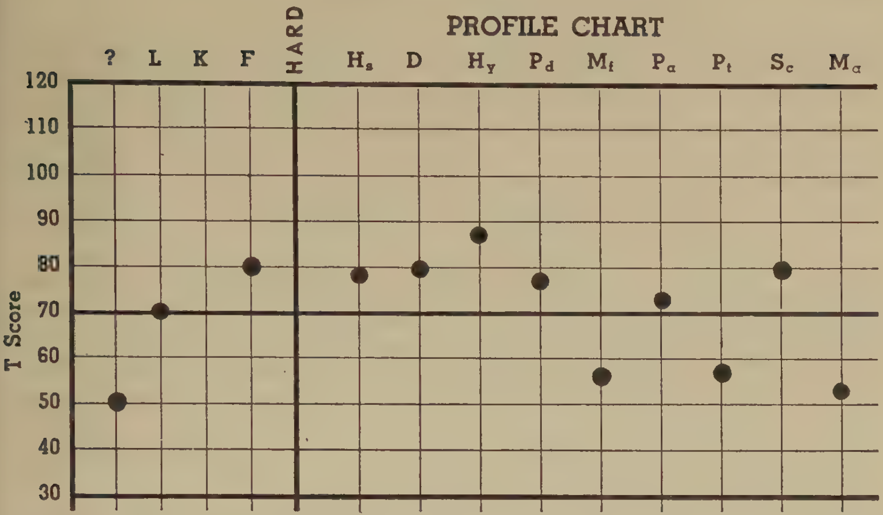

CHART 11. H. A. R. D., female, unmarried, age 44, duration of illness 6 years. Not aided by any form of therapy.

of necessity ordained by (1) the severity and nature of the somatic symptoms; (2) the vested interests of the family, which are also modified by the new situation; (3) the previous adaptive structure of the patient; and (4) the attitudes of the numerous physicians who enter the situation, whose methods may vary from threats of therapeutic nihilism to promises of mystical healing. Certainly, an intermediate position by the physician is desirable. One way to achieve this intermediate position is to give the patient some insight without too much threat. Attainment of this possibility is facilitated by use of the Minnesota Personality Inventory, which guides the physician in his treatment not only of physical symptoms but also of the distorted adaptive means of the patient usually forced into a progressively regressive type of behavior.

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METABOLIC CHARACTERISTICS OF MULTIPLE SCLEROSIS: CHEMICAL ABNORMALITIES IN THE BLOOD AND URINE OF A LARGE SERIES OF PATIENTS AND METABOLIC BALANCE IN TWO PATIENTS*

By Harold H. Jones, Harold H. Jones, Jr., Richard R. Howard,
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We propose to present the results of a five-year investigation of the metabolic pattern in multiple sclerosis. In 1950, we[1] reported that, in this disease, there is an abnormal response to oral glucose, the most striking evidence of which is an elevation of blood pyruvic acid out of proportion to lactic acid. In the fasting serum samples, inorganic phosphorus was significantly lower than in healthy controls. Other significant differences from the normal observed during the glucose stress test have been a lowered sugar tolerance and a relative increase in urine phosphorus and total nitrogen excretion after glucose. This line of investigation has been continued and expanded in an attempt to learn more of the metabolic interrelationships occurring in multiple sclerosis. In two patients, metabolic balance of N, Ca, P, Na, and K were studied, and the effects of glucose, ACTH, and thiamine on metabolic balance were measured. As the mass of data has been taken, a few features have appeared with sufficient regularity to suggest a pattern of metabolism characteristic of multiple sclerosis.

Methods and Materials

A total of 135 consecutive multiple sclerosis patients have been evaluated biochemically, as they came for medical attention. New patients were subjected to a four-hour glucose stress test as previously described by Jones, Jones, and Bunch.[1] The effects of different therapeutic agents and the effects of spontaneous clinical changes on the numerous blood constituents were studied by serial analyses of fasting blood samples at frequent intervals. Data from healthy controls, matched for age and sex with the multiple sclerosis group, were taken concurrently with that of the patients. During the course of the investigation, the effects of glucose on serum total cholesterol,[1] cholesterol esters,[1] total lipid phosphorus,[2] uric acid,[3] and blood labile phosphorus[4] have have determined, in addition to those blood and urine changes previously reported by us. As it became evident that the concentration of a particular substance was not changed significantly in either patients or controls during the glucose stress test, the hourly determination of that substance was discontinued. However, analyses of fasting blood samples were continued until the series of patients and of controls were large enough to allow accurate group comparison.

The analytic procedures used are the same as those previously reported,[1] except as additions or modifications are noted. Adenosine triphosphatase (ATPase) activities at pH 4.8 (acid) and pH 8.9 (alkaline) were determined in fasting serum only, by an adaptation of the procedure of Meister.[5] The

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* Aided by a grant from the National Multiple Sclerosis Society.

adenosine triphosphate, sodium, used as substrate in these analyses was supplied through the courtesy of M. C. Ziporyn, M.D., of the Armour Laboratories. One ATPase unit equals the mgm. of inorganic phosphorus liberated by 100 ml. serum from adenosine triphosphate, sodium, in two hours under the conditions specified by Meister.[5] Total lipid phosphorus and the lecithin, cephalin, and sphingomyelin phosphorus fractions of whole blood and plasma were studied in 23 multiple-sclerosis patients and 25 healthy controls. For these analyses the choline-containing phospholipids were separated from the noncholine-containing phospholipids by the method of Taurog, Entenman, Fries, and Chaikoff.[6] The selective hydrolysis of lecithin, as reported by Zilversmit, Entenman, and Chaikoff[7] was used to differentiate between lecithin and sphingomyelin. Phosphorus analyses were done by the Horecker and Haas[2c] modification of the Fiske and SubbaRow[2b] technique.

In the first balance study, patient L. C., a 51-year-old female, was the subject. Her first symptoms of multiple sclerosis appeared seven to eight years before this study. Her clinical course had been one of very slow progression, with no definite remissions. At the time of this study, she was able to walk with the assistance of one individual. In this patient, the effects of thiamine hydrochloride, given intravenously, and ACTH, given intramuscularly, were observed. Patient M. E., a 36-year-old female, was the subject in the second balance study. The onset of the disease had occurred approximately 14 years before this study. Her disability had been slowly progressive so that she had been unable to walk for two years. In this patient, the effects of glucose, given orally, and thiamine hydrochloride, given intravenously, on metabolic balance were observed. The sequence, dosage, and duration of treatments in the two studies are indicated in the graphs showing the results (FIGURES 5 and 6).

In the metabolic balance studies, the daily diet for each patient remained unchanged throughout the study. Sample diets were analyzed for N, P, Ca, K, and Na. Urinary excretions of these same substances, Cl, creatinine, creatine, and 17-ketosteroids[8a, b] were measured in daily samples. Fecal excretion of N, Ca, P, K, and Na was determined on each three-day pool. Each patient was weighed and a blood sample drawn before food, the first day of each period. In both studies, a metabolic period was three days long. The methods used for blood and urine analyses are the same as those previously cited by Jones *et al.*[1] The plan of the balance studies and the presentation of data closely follow the suggestions of Reifenstein, Albright, and Wells.[9]

Results

Protein Metabolism. TABLE 1 gives the mean values for serum total proteins, albumin and albumin/globulin ratio in a group of 111 healthy controls, 59 multiple sclerosis patients having the remissive type disease and 71 patients having the slowly progressive type disease. Serum total proteins, albumin and albumin/globulin ratio are significantly lower, at the 1 per cent level, in either multiple sclerosis group, than in the controls.

FIGURE 1 shows individual data for serum cholinesterase (ChE) activity in 65 multiple sclerosis patients (35 men and 30 women) having the slowly progressive type disease and 57 patients (16 men and 41 women) having the remissive type. For comparison, the mean value with standard deviation (2.32 ± 0.34) is shown for 122 healthy controls. The occurrence of values above the expected normal is more frequent in the slowly progressive group than in the remissive group, especially in men. Also in the slowly progressive group, the occurrence of values below the expected normal (2.0) is frequent. Most of the individuals showing the abnormally low values are also suffering from poor nutrition, incident to inadequate nursing care. The increased frequency of ChE values above 3.0 in men having the slowly progressive type disease is statistically significant (Chi square = 7.8). The increased incidence of ChE values below 2.0 in this same group of men is also significant (Chi square = 8.25).

In the remissive type disease, the occurrence of abnormally high ChE activity

TABLE 1

MEAN SERUM TOTAL PROTEINS, ALBUMIN AND A/G RATIO, ± S.D.

	T.P.	Alb.	A/G ratio
	gms/100 ml	*gms/100 ml.*	*gm/gm*
111 healthy controls	6.44 ± 0.340	4.40 ± 0.386	2.22 ± 0.444
59 remissive M.S.	6.24 ± 0.374	4.14 ± 0.295	2.01 ± 0.364
"T"*	3.42	4.92	3.30
"P"	<0.01	<0.01	<0.01
71 slowly progressive M.S.	6.28 ± 0.422	4.09 ± 0.351	1.91 ± 0.382
"T"*	2.69	5.60	5.10
"P"	0.01	<0.01	<0.01

* "T" = M.S. group vs. control group.

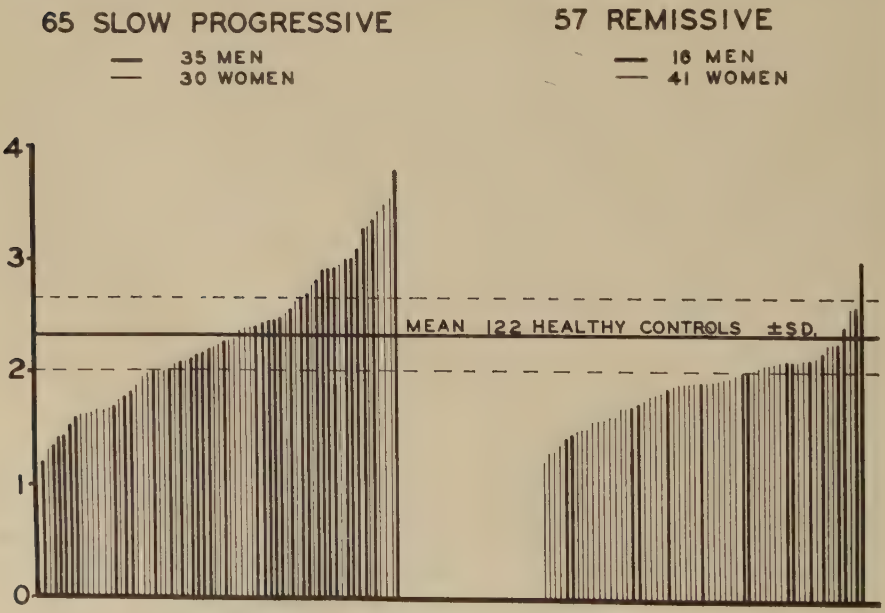

FIGURE 1. Serum cholinesterase in multiple sclerosis.

TABLE 2

COEFFICIENT OF CORRELATION (PEARSONS) BETWEEN SERUM CHE AND SERUM ALBUMIN

Group	No. of pairs of values	No. of individuals	Coeff. of corr. ± S.E.	Remarks
Healthy controls ChE below 2.0	71	42	−0.133 ± 0.117	No correlation
M.S., remissive ChE below 2.0	84	38	+0.133 ± 0.107	No correlation
M.S., slowly progressive ChE below 2.0	63	32	+0.236 ± 0.119	No correlation
Cardiovascular diseases ChE below 2.0	36	36	+0.390 ± 0.102	Sig. + correlation
Misc. carcinomas all ChE values	76	32	+0.400 ± 0.100	Sig. + correlation
Misc. general surgical patients ChE below 2.0	283	99	+0.530 ± 0.040	Sig. + correlation
Surgical patients undergoing biliary tract surgery all ChE values	146	44	+0.400 ± 0.070	Sig. + correlation

TABLE 3

CEPHALIN FLOCCULATION IN FASTING SERUM (ALL RESULTS AFTER 48 HRS)

	Neg.	+	++	+++	++++
120 M.S. patients	66	21	17	8	8
91 healthy controls	77	10	4	0	0

is rare in either men or women. The observation of values below normal is common. The increased incidence of values below 2.0 in either males or females afflicted by the remissive type disease is significant (Chi square for males = 9.52; for females = 25.8).

In pathological conditions other than neurological, serum ChE activity parallels serum albumin concentration. As data were taken on these two serum characteristics in multiple sclerosis patients, there did not seem to be any direct relationship between serum albumin and ChE. Coefficients of correlation between these two variables were calculated for a series of multiple sclerosis patients, healthy and pathological controls. TABLE 2 gives the results of these calculations.

Liver function tests. TABLE 3 shows the results of serum cephalin flocculation tests in 120 multiple sclerosis patients (57 remissive and 63 slowly progressive) and 91 healthy controls. The results on the patients are those obtained during their first biochemical evaluation. Data for the multiple sclerosis patients are not subdivided according to "remissive" or "slowly progressive" since there was no difference in the occurrence of abnormal values between the two types. The increased incidence of positive cephalin flocculation tests (any degree) in the multiple sclerosis patients as compared to the controls is statistically significant.

Serum thymol turbidity values were elevated in a significant number of multiple-sclerosis patients, but the occurrence of this abnormality was not as common as in abnormal cephalin flocculation tests. Twenty-one of 44 multiple sclerosis patients had thymol turbidity values above 1.0, compared to 11 out of 52 healthy controls with values above 1.0. The mean value for the 52 controls was 0.59 (range 0–1.38); that for 44 multiple sclerosis patients was 1.08 (range 0–3.83).

Ninety out of 102 consecutive, relatively untreated, multiple sclerosis patients had prothrombin time values longer than that for pooled plasma from healthy controls. These data are shown in FIGURE 2. Of the 12 patients showing prothrombin time values 100 per cent or more of the pooled control value, 10 were of the slowly progressive type with extensive impairment. The eight patients shown as "parallel diseases" are four patients having amyotrophic lateral sclerosis and four having olivopontocerebellar atrophy.

Serum bilirubin and serum alkaline phosphatase values in multiple sclerosis patients are consistently within normal limits. Bromsulfalein retention studies have not been done.

Blood labile phosphorus and serum ATPase. Blood labile phosphorus levels were determined in freshly drawn heparinized blood by measuring the amount of inorganic phosphorus liberated from a protein free filtrate by 1 N HCL at 100° C. in 15 minutes. This procedure has been shown to be valid as an estimate of adenosine triphosphate concentrations.[10] The mean labile phosphorus values are higher in multiple sclerosis patients than in healthy controls (TABLE

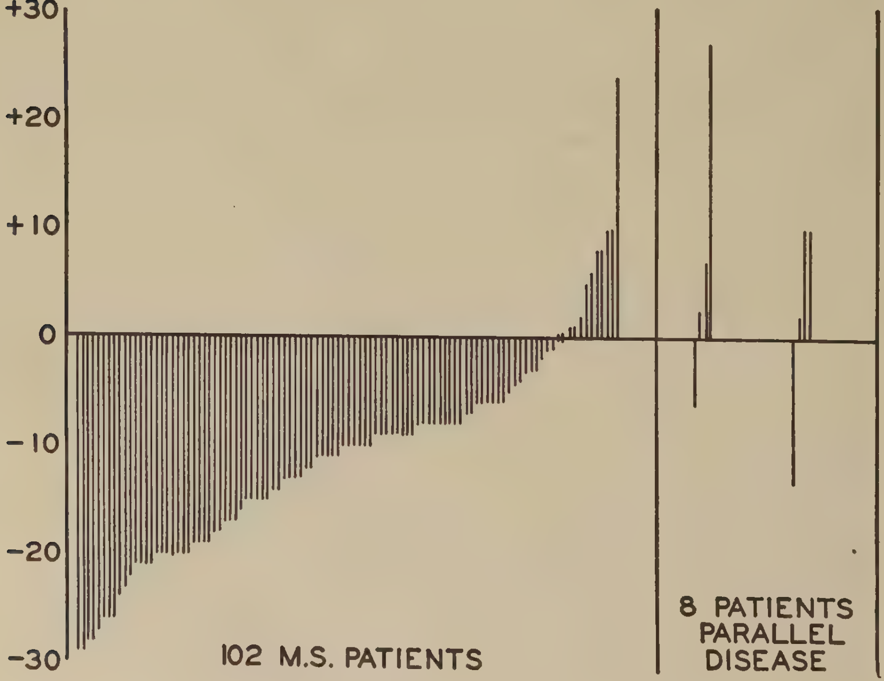

FIGURE 2. Prothrombin time per cent difference healthy controls.

TABLE 4

BLOOD LABILE PHOSPHORUS (MGM. LABILE P/100 ML. BLOOD)

Group	No.	Range	Mean	± S.D.	"T"	"P"
M.S.	55	3.90–7.00	5.11	0.786	3.1	<0.01
Healthy controls	60	3.40–5.80	4.71	0.590		

4). In general, the highest labile phosphorus values have been observed during an active phase of the disease.

At pH 4.8 serum ATPase activity is significantly lower in multiple sclerosis patients than in healthy controls. The mean value for 51 multiple sclerosis patients was 1.95 units (S. D. ±0.55), while the corresponding value for 58 healthy controls was 2.69 (S. D. ±0.94). The difference between the mean values is statistically significant at the 1 per cent level. FIGURE 3 shows the individual values for the multiple sclerosis patients, along with the mean normal value and standard deviation. There was no significant difference between the average ATPase values at pH 8.9 for 26 multiple sclerosis patients and 32 healthy controls. Blood labile phosphorus and serum acid ATPase values determined on the same blood samples are not related to each other by mathematical correlation.

The effects of various therapeutic agents on serum acid ATPase have been investigated. Fourteen of 18 patients receiving 250-500 ml. of fresh whole blood by transfusion showed an increase in acid ATPase 24 hours after transfusion. Four out of five patients given serum albumin intravenously had an increase in this enzyme 24 to 48 hours later. These data are shown in FIGURE 4. The effects of ACTH or ACTH and insulin on serum acid ATPase were studied in four patients. In each instance, the medication gave considerable symptomatic relief and a significant increase in enzyme activity was found.

Blood lipids. That serum total cholesterol and cholesterol esters are elevated in multiple sclerosis has been reported by Jones *et al.*[1] The average serum total lipid phosphorus was not significantly different for 105 multiple sclerosis patients than for 80 healthy controls. The mean value for the multiple sclerosis group was 9.78 mgm./100 ml. (S. D. ±1.39). The corresponding value for the control group was 10.03 (S. D. ±1.58). In addition to these studies of serum total lipid phosphorus, the lecithin, cephalin, sphingomyelin, and total lipid phosphorus contents of plasma and whole blood were determined for 23 multiple sclerosis patients and 25 healthy controls (patients and controls matched for age and sex). No differences in any of the phospholipid fractions were observed between the two groups. Serial analyses of total and fractional phospholipids were made in seven patients over a period of 12 months. No significant change within the individual in the lecithin, cephalin, or sphingomyelin content of plasma or whole blood was found during this time.

Calcium metabolism. The most striking observation during the balance studies was the tendency of both patients to be in negative Ca balance. Calcium balance data for patient L. C. is shown in FIGURE 5, that for patient M. E. in FIGURE 6. During the control periods at the beginning of both studies, the patients were in negative Ca balance (Ca intake for L. C. was 530 mgm./day; Ca intake for M. E., 660 mgm./day). During the three days that thiamine hydrochloride, 300 mgm. intravenously/day, was given L. C., there was a decrease in urinary Ca. At this same time, however, there was an increase in fecal Ca so that the net effect was negative Ca balance. In patient M. E., the effects of thiamine on Ca balance could be better evaluated since she was given 200 mgm. of thiamine hydrochloride intravenously twice daily for 12 days. In this second patient, urinary Ca did not change appreciably with thiamine. Fecal Ca decreased from control values (periods 1 and 2) of 687 and 800 mgm./24

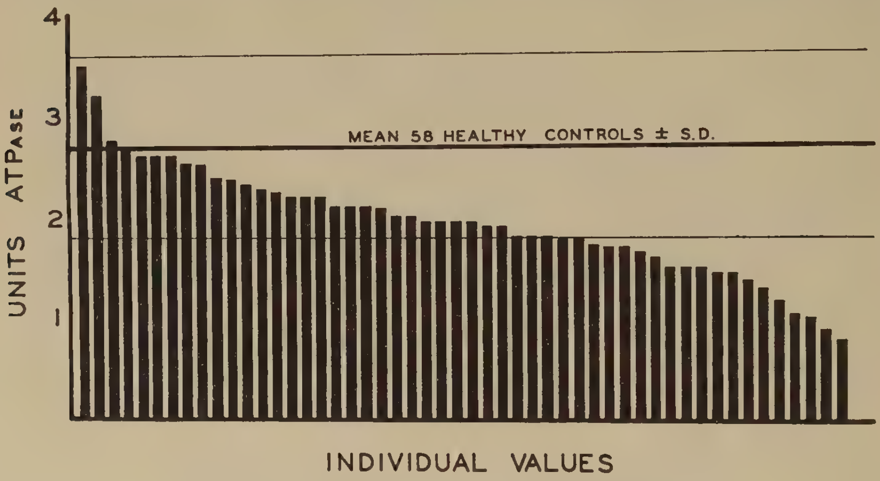

FIGURE 3. Serum acid ATPase. Fifty-one multiple-sclerosis patients.

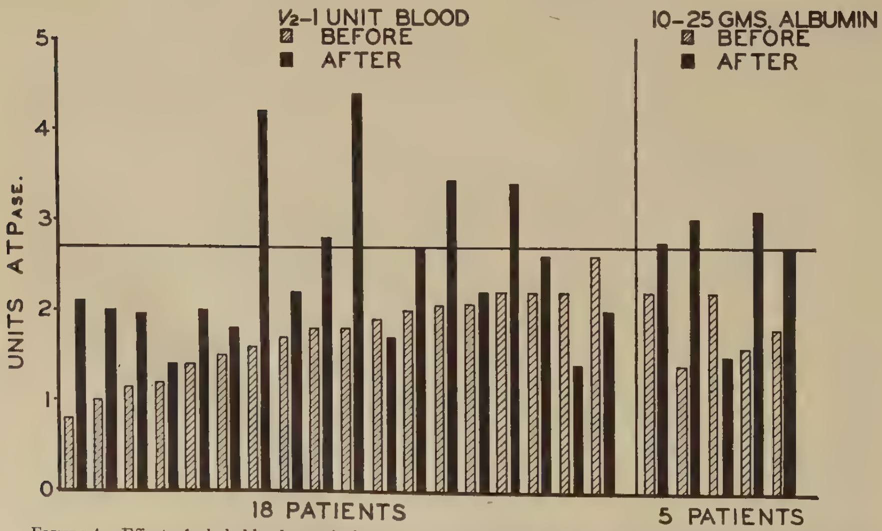

FIGURE 4. Effect of whole blood transfusion or of human albumin on serum acid ATPase in multiple sclerosis.

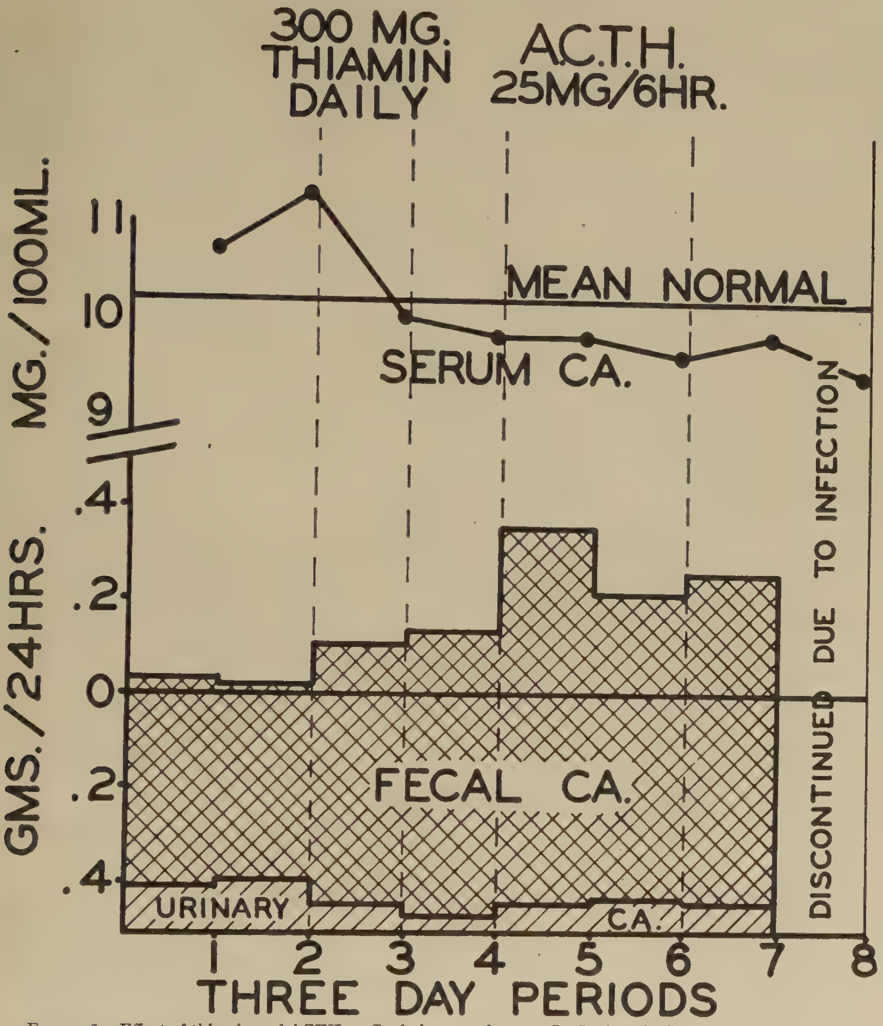

FIGURE 5. Effect of thiamin and ACTH on Ca. balance and serum Ca. Patient L. C.

hrs. to 496 mgm./24 hrs., the first three days on thiamine (period 6) and there after to 301, 274, and 270 mgm./24 hrs. in periods 7, 8, and 9. By the second period on thiamine, this patient was in positive Ca balance for the first time during the study. In both patients, serum Ca fell with thiamine administration. When thiamine was discontinued fecal Ca increased in both patients, especially in M. E.

There was an increase in urinary and fecal Ca in L. C. during the course of ACTH. When the drug was discontinued, urinary Ca decreased after the first 24 hours. With ACTH administration, this patient exhibited the changes in all phases of metabolism that would have been expected in a normal individual.

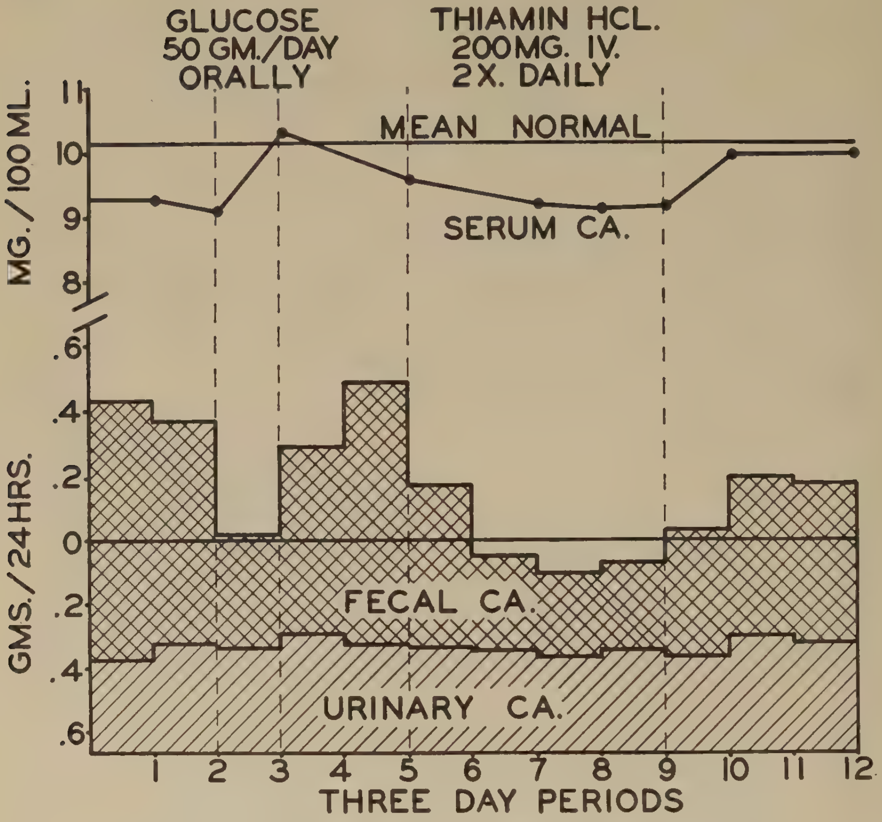

FIGURE 6. The effect of glucose and thiamin on Ca. balance and serum Ca. Patient M. E.

Fifty grams of oral glucose daily for three days resulted in a decrease in fecal Ca in patient M. E. (FIGURE 6, period 3). Calcium balance averaged −10 mgm./24 hrs. for this period. Preceding control values for Ca balance had been −424 and −365 mgm./24 hrs. With glucose, serum Ca increased from 9.1 to 10.3 mgm./100 ml.

Both patients were in positive N balance at the beginning of the studies. Nitrogen balance was not altered significantly by thiamine in either patient. With 50 grams of oral glucose per day for three days, N retention was increased in patient M. E.

There was a decrease in P excretion during the thiamine regimen and an increase in P excretion when thiamine was discontinued. Changes in P balance in both cases agreed well with those expected from the changes in N and Ca.

Miscellaneous negative data. Other blood variables studied have been serum uric acid, Na, K, CO_2, and Cl. As a group, multiple sclerosis patients did not exhibit abnormal values for any of these blood constituents. In the two balance studies in multiple sclerosis patients, Na and K balance and Cl and 17-

ketosteroid excretion were not abnormal. Twenty-four hour urine samples were analyzed for 17-ketosteroids in a large group of patients and controls. The results were not characteristically different in the multiple sclerosis group, the majority being within the normal limits, taking into account the age and sex of the patients.

Discussion

Low serum albumin, low albumin/globulin ratio, positive cephalin flocculation test, elevated thymol turbidity index, and prolonged prothrombin time value in multiple sclerosis could be interpreted as impaired liver function (Volk, Saifer, and Rabiner[11] have observed similar abnormalities in serum in this disease). Those multiple sclerosis patients having low serum ChE activity as well as the above signs of liver damage strengthen such an interpretation. The use of serum ChE as a liver function test has been reported by numerous investigators.[12, 13] The frequent occurrence, however, of abnormally high serum ChE activity in multiple sclerosis patients having low serum albumin and other biochemical signs of liver damage is an enigma. High serum ChE activities are little understood other than in the nephrotic syndrome.[14] The lack of correlation between serum ChE (below 2.0) and serum albumin in multiple sclerosis patients is in contrast to the positive correlation observed in general medical and surgical patients.[12, 15] This contrast is further evidence of abnormal protein metabolism in multiple sclerosis but the nature of the error is not known.

In spite of our negative findings in lecithin, cephalin, and sphingomyelin phosphorus concentrations in plasma and whole blood, we believe further studies on lipids are indicated. Fisk, Chanutin, and Klingman[16] reported an increased sphingomyelin concentration in a miscellaneous group of neurological patients, including some patients having demyelinating disorders. The whole picture of lipid metabolism, including enzymes, coenzymes, and intermediate metabolites needs to be investigated.

Interpretations of high blood labile phosphorus levels and low serum ATPase activity at pH 4.8 in multiple sclerosis patients are not now apparent. We need to know how these derangements in the adenosine triphosphate system are related to the observed abnormalities in carbohydrate metabolism.

To what extent negative Ca balance occurs in multiple sclerosis is not known. Inactivity may be a big factor in the negative balances encountered in this study. Whether thiamine alters Ca balance by increasing Ca absorption or by some more direct effect on bone metabolism is unknown. The favorable effects of glucose on N, Ca, and P balance are of special interest in view of the previously observed abnormal intermediate metabolism of glucose in multiple sclerosis.[1] Certainly, additional investigation is needed to determine optimum dietary management in this disease.

The use of biochemical data in clinical management of multiple sclerosis patients. As frequent biochemical data were taken on the same individuals, it was noted that serum albumin, albumin/globulin ratio, and ChE activity consistently fluctuated with symptomatology. Decreases in these values, all indicative of changes in protein metabolism, either preceded or accompanied exacerbation and increases occurred with clinical improvement. These serum levels have proved helpful in evaluating the importance of minor increases in symptoms which a patient frequently experiences before any well-defined clinical change can be seen. Whole-blood transfusion or human albumin, intravenously, quickly increases serum albumin, albumin/globulin ratio, and ChE levels in the patients and gives symptomatic relief in many instances. We believe that the clinical course of a group of multiple sclerosis patients, especially those having the remissive type disease, has been improved by the early use of whole blood or human albumin as the need is indicated by a decrease in serum albumin or ChE activity. To some extent hemoglobin levels help decide which agent is to be preferred. Other measures altering nitrogen balance, as rest, insulin, or increased protein in the diet, favorably influence the biochemical picture and clinical status of patients, but the effects of these agents are delayed as compared to blood or albumin.

With the limited experience we have had with serum acid ATPase activity, it appears that this enzyme may also fluctuate with symptomatology. Other biochemical abnormalities reported here are chiefly of use in establishing diagnosis or as they contribute to the development of the metabolic picture in the disease.

Summary

An investigation of the metabolic pattern in multiple sclerosis has shown the following significant features:

(1) There is an abnormal biochemical response to oral glucose, the most striking evidence of which is an elevation of pyruvic acid out of proportion to lactic acid. Serum inorganic phosphorus is lower in the fasting sample. Following glucose, the decrease in serum inorganic phosphorus is less in multiple sclerosis patients than in healthy controls.

(2) Serum albumin and albumin/globulin ratio are low. Serum ChE values above the expected normal are frequently observed in men having the slowly progressive type disease. Values below normal are common in individuals with the remissive type.

(3) The regularity with which some prolongation of prothrombin time values, positive cephalin flocculation tests, and increased thymol turbidity indices are found in multiple sclerosis patients suggests some impairment of liver function.

(4) Serum acid ATPase activity is low and is increased by blood transfusion, human albumin, and other therapeutic agents.

(5) In the two metabolic balance studies done in two patients, both individuals tended to be in negative Ca balance. Intravenous thiamine resulted in Ca retention.

(6) Changes in serum albumin, albumin/globulin ratio, and ChE values within an individual have been found of practical importance in the clinical management of multiple sclerosis. Impending exacerbations are indicated by decreases in one or all of these constituents. The values are quickly returned

to higher levels by whole blood or human albumin and it is believed that such therapy aborts relapses in some patients.

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THE DIAGNOSIS OF MULTIPLE SCLEROSIS

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The diagnosis of multiple sclerosis and its differentiation from other diseases is not difficult in most patients. The diagnosis, however, cannot be made simply, and it constitutes a problem in the minority of instances for the specialist and in a larger number of cases for the nonspecialist. Little fresh information can be added to what the experienced neurologist already knows concerning the diagnosis of multiple sclerosis. It is conceivable that newer knowledge about biochemical patterns in the disease may ultimately be of more specific diagnostic value. These newer data which have been extensively discussed in other papers in this monograph will be referred to below. At this time, renewed emphasis may be placed on certain aspects of diagnosis which, though long familiar, are important, especially to those less experienced in the disease.

The major criteria for diagnosis are clinical, based on the history and the physical findings, with inconstantly present laboratory deviations providing important but not confirmatory evidence. As aptly phrased by Doctor Denny-Brown, the difficulty of diagnosis lies in our "present inability to estimate the disease in life by any other means than the neurologic disorder it produces."

What is the neurological disorder it produces? How characteristic is the syndrome of multiple sclerosis? To those who have dealt much with the disease the pattern seems so characteristic as to be almost unmistakable. Even so, the pattern does not easily lend itself to precise definition. Thus, despite the neurologists' claim of a characteristic pattern, multiple sclerosis may begin suddenly with a relatively minor symptom of transient duration, such as visual blurring of an eye, weakness or paresthesia of a limb, or clumsiness and awkwardness in the use of a hand, to be followed by an interval of well-being for weeks, months, or years, before the development of further symptoms; or it may begin insidiously with gradually developing disabilities that persist without remissions and only minor fluctuations, the chief manifestation often taking the form of a steadily progressive gait impairment. In rarer instances, a third mode of onset characterized by explosive severity may initiate the disease, which then takes the form of an acute, fulminating, massively incapacitating illness, involving paralysis or severe weakness of limbs accompanied by severe, widespread numbness, incoordination, blindness in one or both eyes, speech and bladder difficulties, and mental clouding to the point of stupor. Such an onset might lead to death shortly, go on to complete recovery followed by later recurrences, or result in partial recovery accompanied by residual symptoms and subsequent exacerbations.

With such apparent wide differences in symptomatology and course, what are the essential criteria which guide the clinician in making the diagnosis of multiple sclerosis? There are exceptions but, in general, the diagnosis cannot be made with assurance unless one, or preferably both, of two criteria be fulfilled.

The first criterion is concerned with the history of the development of symptoms and subsequent progress of the disease after the illness comes under observation. The alleviation or total remission of symptoms or signs, whether single or multiple, even when the dysfunction is an isolated first manifestation, assuming that other causes are undiscoverable, creates the presumption of multiple sclerosis. Certain common locations for first symptoms, such as blurring of vision in one or both eyes, numbness, paresthesiae and clumsiness, stiffness, weakness, and awkwardness of one or more limbs, often asymmetrically, heighten the presumption. If alleviation is followed by recurrence, especially when other sites are involved, the diagnosis becomes highly probable. The diagnosis is not ruled out, however, if a fresh outbreak has not manifested itself, even years later or, on the contrary, if a steadily progressive downhill course ensues which, if closely observed, almost always reveals minor fluctuations.

The second criterion is that there be unequivocal evidence, based on neurologic signs, of separate discrete lesions in scattered areas of the nervous system. The diagnosis of any structural nervous system disease, especially of multiple sclerosis, is properly made only by first localizing the site or sites of the lesions. To arrive at a diagnosis merely on the basis of the occurrence of certain signs, such as nystagmus, intention tremor, or dysarthria, without a clear visualization of the meaning of such dysfunctions in terms of the site of the lesion within the central nervous system, is hazardous, and diagnosis on the basis of symptoms alone is inexcusable. Thus, clear demonstration of disseminated foci of structural defects in the white matter is a most important step in establishing the diagnosis. A diagnosis of multiple sclerosis made on the basis of a single isolated dysfunction owing to a single lesion must remain presumptive pending the subsequent course of events. If the neurologic signs are symmetric, suggesting diffuse lesions confined to the long ascending and descending tracts of the cord or to the cerebral white matter, the diagnosis again may remain in doubt until time brings into the picture neurologic evidence of additional separate focal lesions.

Though individual symptoms and signs or certain combinations of them are quite characteristic of multiple sclerosis by virtue of the predilection of the lesions for certain areas, notably the pyramidal tracts and posterior columns of the spinal cord, the posterior longitudinal bundle and cerebellar connections of the brain stem, the frontal subcortical white matter of the cerebrum and the optic nerves (actually not nerves but tracts), no individual sign or group of findings is pathognomonic. All such manifestations reflect sites of lesions rather than their nature, and may be caused by other diseases acting at these sites as well. Nevertheless, from the course of the illness longitudinally and from the distribution of the neurologic defects cross-sectionally, strong inferences may be made as to the probable nature of the lesion, namely, the acute inflammatory or chronic gliotic plaque of multiple sclerosis.

Additional aid in the diagnosis of the type of structural defect of the nervous system is derived from laboratory tests. No specific diagnostic test for multiple sclerosis is available. None of the abnormal laboratory results found in multiple sclerosis is present in all cases and none is pathognomonic of the specific lesion of the disease. Routine blood and urine studies, including chemical and serologic reactions, are normal. The electroencephalogram shows moderate abnormalities which are diffuse and nonspecific in 50 to 80 per cent of series which have been reported. Pneumoencephalograms show symmetric or asymmetric cerebral atrophy of slight to moderate degree in moderately advanced cases, but this nonspecific finding does not warrant the use of the procedure as a routine diagnostic test. If one looks upon multiple sclerosis as the commonest cause of retrobulbar neuropathy of the optic nerve, then routine testing of the central visual fields should be carried out, since the finding of central and paracentral scotomas provides indirect support but no proof of the existence of multiple sclerosis.

Examination of the cerebrospinal fluid is sometimes of value in the diagnosis of multiple sclerosis and should be carried out routinely. In differential diagnosis, however, a normal spinal fluid often enhances the probability of multiple sclerosis rather than the reverse. It is said that some change in the cerebrospinal fluid is present in three quarters of the cases of multiple sclerosis. However, analyses of such data show that, among the routine tests, average values for protein level and cell count are actually normal, and that elevation of either one of these occurs in only one third of the cases. In one very large series, accordingly, only 35 per cent of the patients had a leukocyte count in the spinal fluid of over five per cubic millimeter and, in another series, only 8 per cent had a count of over ten per cubic millimeter. Protein contents of the spinal fluid over 45 mgm. per 100 cc. were reported in only 33 per cent and 36 per cent respectively of the cases in these two series. Colloidal gold reactions of the cerebrospinal fluid when carried out by the usual method available in most hospitals have shown deviations from the normal in one third to two thirds of the cases in various series reported. The first zone elevation of the colloidal gold reaction is present probably in not more than one quarter of the cases. By a new and refined technique of colloidal gold testing not yet in common use in hospitals, a characteristic so-called Type D reaction has been reported in 83 per cent of the cases. The reaction, however, cannot be considered pathognomonic.

In the search for clues as to pathogenesis, the current intensive investigations of biochemical changes in multiple sclerosis have revealed abnormalities in metabolic balance studies and abnormal concentrations of various constituents of blood and spinal fluid, especially protein fractions. Many of these changes have already been discussed in detail in this monograph, but as yet no deviation has been claimed to be pathognomonic. Whether certain characteristic abnormal results, such as the consistently found elevation of gamma globulin in the spinal fluid by various workers using different techniques, will lead to practical diagnostic tests supporting the diagnosis of multiple sclerosis, and whether these tests will be found feasible in general hospital laboratories is not yet known, but both conjectures seem likely. Specific serologic tests have been described for many years, and efforts continue to be made in this direction, but a reliable test has as yet not been devised.

Specialized techniques have shown changes in certain functions such as increase in capillary permeability and increase in the adhesiveness of blood platelets in the majority of patients. Though not specific for multiple sclerosis, the finding of such changes may lend support to the diagnosis in hospitals where the facilities for such tests are available.

Diagnosis of diseases related to multiple sclerosis is a misnomer, since it is uncertain whether other diseases having prominent features of demyelination are actually related to multiple sclerosis either in terms of etiology of pathogenesis. Of great importance, however, is differential diagnosis in connection with diseases which, in cross section, at any given time might resemble multiple sclerosis. This problem is concerned especially with two patterns of clinical manifestations which multiple sclerosis may assume, namely, that of the diffuse degenerative system disease and that of a level lesion when a single large plaque is present in the spinal cord or even in the brain. A differentiation may be difficult to make on clinical grounds alone for reasons already stated. When such clinical patterns are manifested by patients suspected of having multiple sclerosis, it is therefore necessary to rule out other disease by appropriate laboratory studies.

The tract degenerations of subacute combined sclerosis, tabes (or taboparesis) and diabetic myelopathy are usually easily differentiated by means of tests which need not be listed here. Those of heredodegenerative diseases, such as Friedreich's ataxia, progressive cerebellar degeneration, and other members of this group cannot be differentiated by laboratory tests, save for the possible occurrence of abnormality of the cerebrospinal fluid in multiple sclerosis, but may be set apart by the occurrence of family history of similar disease and, in the case of Friedreich's ataxia, by the early age of onset.

In the case of nervous-system diseases producing level lesions, especially of the spinal cord, much has been made of the danger of misdiagnosing intraspinal mass lesions as multiple sclerosis. Several series of such cases have been reported. However, in reviewing the clinical manifestations of these reported cases, it is apparent that the mistakes have occurred largely through ignoring fundamental and well-known principles of diagnosis; and such mistakes, moreover, have rarely been made by competent physicians. It is obvious, when level signs indicating a local intraspinal lesion are present and few or no neurologic abnormalities are present above that level, that steps must be taken to rule out spinal cord compression before one can accept the cause as transverse myelopathy caused by a plaque of multiple sclerosis. These steps include radiographs of the spine and manometric determinations of the cerebrospinal fluid dynamics. It must be emphasized that only bilateral jugular compression is of value in ruling out or establishing the presence of an intraspinal subarachnoid block, since pressure rises may occur with perfect normality within the manometer on abdominal straining or coughing even in the presence of a subarachnoid block. The spinal fluid protein content is of great importance here, since compressing lesions, especially tumors, are associated with a much higher protein content generally than is multiple sclerosis. Myelography should probably be done in all patients who have no abnormal signs above a spinal level.

Acutely developing, widespread symptoms (assuming that obvious causes such as preceding exanthem or vaccination are not present) always raises the question whether the illness is a separate entity of acute inflammatory nature thought to be attributable to virus invasion, namely, idiopathic acute disseminated encephalomyelitis. Because of the present unsettled controversy reregarding the identity of this condition with acute multiple sclerosis, the differentiation is of value only in attempting a prognosis. Proponents of the hypothesis that the diseases are separate entities insist that encephalomyelitis is confined to a single self-limited episode which, if not fatal, leads either to complete recovery or chronic static residua, but not to subsequent progression, either steady or fluctuant. On the basis of present concepts, features of a first massive episode that are more apt to occur in this disease than in acute multiple sclerosis are fever, headache, somnolence, and pains in various locations suggesting radicular involvement. In addition, it is believed that the colloidal gold curve is more often abnormal in multiple sclerosis than in encephalomyelitis, whereas cell counts and total protein values in the cerebrospinal fluid are apt to be higher in encephalomyelitis than in acute multiple sclerosis. In the latter disease, even in acute exacerbations, the fluid may be entirely normal, show lesser increases in cells and protein, or show only a colloidal gold alteration.

In conclusion, it may be said that we stand undoubtedly on the threshold of new biological discoveries concerning multiple sclerosis which will provide not only insight into its fundamental etiology and pathogenesis but a means of identifying it more precisely than has been heretofore available.

PREDICTABILITY OF EXACERBATION AND REMISSION IN MULTIPLE SCLEROSIS*

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The natural history of multiple sclerosis, established by many clinicians' observation of thousands of cases, includes a wide range of possible courses for the individual case. The percentage expectancy in groups of cases, calculated from various bases such as, among others, the first symptom and age at onset, has been broadly established.[1, 2, 3] Attempts have been made to form classifications (according to various criteria) into types and forms of the disease on which a prognostic predictability might be established. The tendency of the disease in its manifold variations to override such definitions has, however, greatly limited the value of such efforts, with the result that, in the final analysis, most reports have represented conclusions based on the clinical judgments of the observers, which were not susceptible of duplication by others, and thus of no significant assistance in general clinical management.

Generally, it is possible to place a patient in one of two main groupings after a period of observation in the early case and usually, from the anamnesis, in one of established status prior to the beginning of observation. These are the actively progressive cases having no observable fluctuation and those which are progressive more slowly, for almost all cases are progressive to a degree, although the progression may be interrupted and sometimes reversed over remarkably long periods by major fluctuation of the neurological and clinical manifestations. In the first group will be found about 25 per cent of the total who may be expected to develop serious disability and invalidism or terminate in the space of a few years.[4, 3] The cases in the second category show widely varying courses extending over many years. In about 17 per cent[4a] of the total, complete or nearly complete remission may be established, sometimes gradually, for periods lasting a great number of years. It has been the frequent observation of clinicians that a strikingly consistent course[5] is characteristic for the individual patient when his case is viewed in retrospect.

We are given, then, a disease having a multiplicity of disabling outcomes possible, a large natural tendency to improvement, or the maintenance of unchanged levels of clinical status for long periods of time, and, at the present time, no demonstrably effective treatment. In such a situation, the physician's obligation to his patient requires that he determine as certainly as possible what expectation may be entertained for the continued activity of the patient, and in what degree. Planning for productive activity in accordance with a predictable degree of disability is of vital importance to the patient, and proper supportive reassurance by the physician may be equally well-based on such prognostic information, if it is available. Such information may serve, moreover, as the basis for a decision as to the efficacy of therapeutic measures.

The evaluation of treatment or the prediction of progress in multiple sclero-

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* Supported by a grant from the National Multiple Sclerosis Society.

sis has generally been controlled by attempts to follow groups of patients to whom certain criteria are applied in an effort to establish the number and degree of fluctuations in disability and clinical or neurological status.[6, 7, 8, 9] Too often this procedure has taken too much account of subjective factors introduced by statements of patients or examiners' impressions, and discrepancies in resulting reports have left only uncertainty. Undoubtedly, different interpretations of the definitions proposed for the purpose of describing the clinical status of a case at a given time has been a factor in the failure of attempts to repeat and confirm investigative studies reported. One of us[7] proposed a method for evaluation of status in multiple sclerosis patients, which depends solely on objective findings of the neurological examination. The result of a given examination is expressed as a numeral which represents the summation of weighted values assigned according to the degree of significance attached to the neurologic abnormalities and the extent of the involvement noted. By this means, it is possible to express the objective clinical status of a patient in such a way that another examiner, at a different time, can promptly determine the quantitative difference of condition as it relates to actual neurological and functional abnormality. Experience with the method over a period of nearly six years has demonstrated its dependability in the observation of patients in the private practice of one of us (L. A.) and those seen in an active outpatient clinic (Boston Multiple Sclerosis Research Clinic).

In order to furnish an easily appreciated picture of individual cases the numerical values for each examination are plotted so that fluctuation in functional competence and degree of neurologic involvement is shown by the curve connecting the points. The relative importance of a given numerical increase or decrease will obviously vary according to number, variety, and degree of abnormal findings, and according to the stage of damage caused by the disease. The ratio chart is therefore used, as this chart expresses the visual story of a case history more correctly than does the usual difference chart. This graphic method utilizes a grid on which the scale of the ordinates is divided in proportion to the logarithms of numbers in an arithmetical progression. The abscissal gradation is in a uniform time scale. It is important here to point out that the data recorded are derived from physical examinations done in such detail as to permit the recording of a quantitative value for each of 50 potential variations from a normal neurologic condition. It is obvious that instances of possibly marked clinical fluctuation may be unrecorded when the interval between examinations is prolonged, but any attempt to interpolate by means of an anamnesis would cancel the value of the method.

A complementary physical finding which would furnish information on the basic activity and integrity of vital processes affecting an individual, without being influenced by the neuropathology of multiple sclerosis seemed to be supplied by the blood pressure level. Blood pressure is recorded for each patient at the time of examination, and the repeated observations in over 200 cases were taken for statistical analysis.[10] Only unquestioned cases of multiple sclerosis were included, and patients afflicted with coexisting cardiovascular, renal, or endocrine disorders which could affect blood pressure were excluded. The essential findings were: (1) multiple sclerosis patients are hypotensive in respect to normal levels for the respective age and sex; (2) the hypotension is not a factor of the degree of activity possible to the patient; in other words, this disorder is not attributable to the sedentary existence which, in a more or less crippled individual, frequently produces a hypotension relative to the levels of the patient's normal. No instances of a postural hypotension have been observed such as have been reported in some types of neurological disease.

No discussion is indicated or proposed at this point which would attempt to explain the physiological reactions present and contributory to the observed hypotension, or the possible association of the condition with any postulated theory of etiology and pathogenesis in multiple sclerosis. Hypotension is simply presented as a basic element in human physical makeup which, in multiple sclerosis patients, shows a significant and constant type of deviation from normal levels. It was considered worth while to make a trial comparison of blood pressure readings with the weighted neurological index of involvement in our patients as an extension and amplification of the method used for assessing clinical status quantitatively.

The resting systolic pressure has been used since pulse pressures were shown to be normal and, for presentation here, only those cases showing no specific extraneous condition affecting blood pressure, though the rare hypertensive seems to show variations comparable to those in patients having no cardiovascular disorder. The pressures are plotted on the same time scale with the neurological value, but they are given an arithmetical value, since the proportional scale does not give an adequate visual expression of changes in level. In some patients a marked lability of unexplained cause was noted. This lability does not usually interfere with the use of resultant curves as parallel observations.

When the blood pressure and examination values are plotted in the manner described, the resultant curves show a very uniform tendency to assume relationships of position which are indicative of the course which a case may be expected to follow. This process may be simply described as follows:

(1) A consistent trend in blood pressure is predictive of a mirrored trend in neurological status (FIGURE 1).

(2) Long-range improvement is accompanied by a steady slight rise in blood pressure level (FIGURE 2), while a long-range retrogression is accompanied by a decline in blood pressure (FIGURE 3).

(3) Paradoxically, a sudden marked rise in blood pressure may generally be taken as indicating that the patient will soon show evidence of temporary deterioration of his neurological status followed by an early remission (FIGURE 4). In other words, rise of blood pressure preceding an exacerbation indicates a favorable prognosis for recovery from that attack.

(4) Rise of blood pressure accompanying an exacerbation likewise indicates a favorable prognosis of the attack (FIGURE 5).

(5) A marked acute deterioration of status not preceded or accompanied by blood pressure rise generally prognosticates an unfavorable course tending to

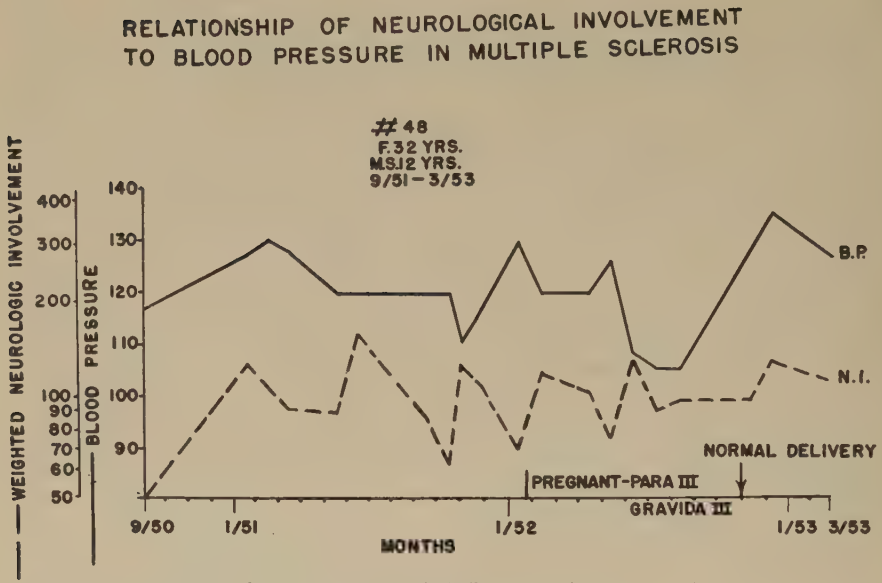

FIGURE 1. #48—WF32. Fluctuant course neurologically, but stable for mean values. Probably active process with prognosis guarded. Blood pressure and neurological curves mirrored.

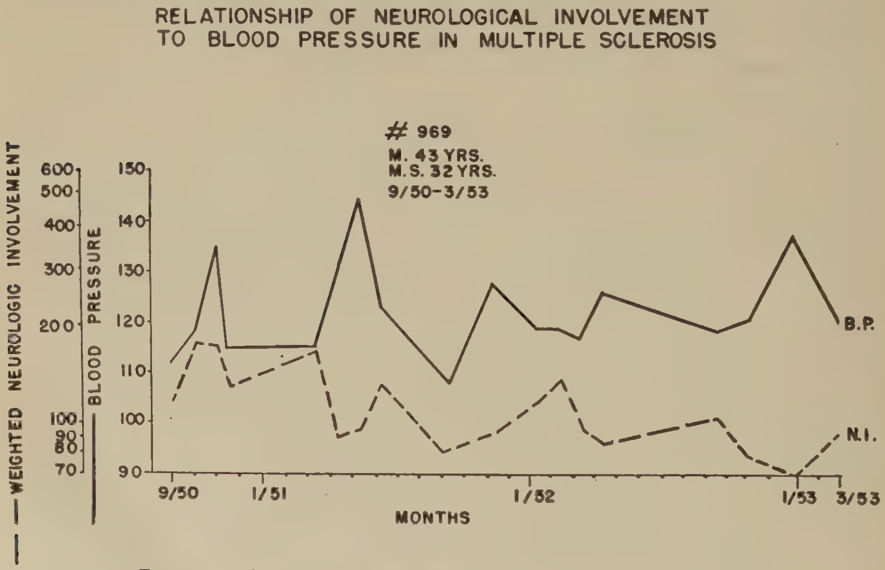

FIGURE 2. #A969—WM43. Improving mildly active case—mirrored curves.

turn into a long-range retrogression (FIGURE 6). A generally stable blood pressure, however, may accompany a relatively nonfluctuant benign clinical course.

(6) Raising or lowering the blood pressure artifically does not necessarily influence the course of the illness significantly (FIGURE 7).

To make the chart most useful, frequent observations are necessary in order

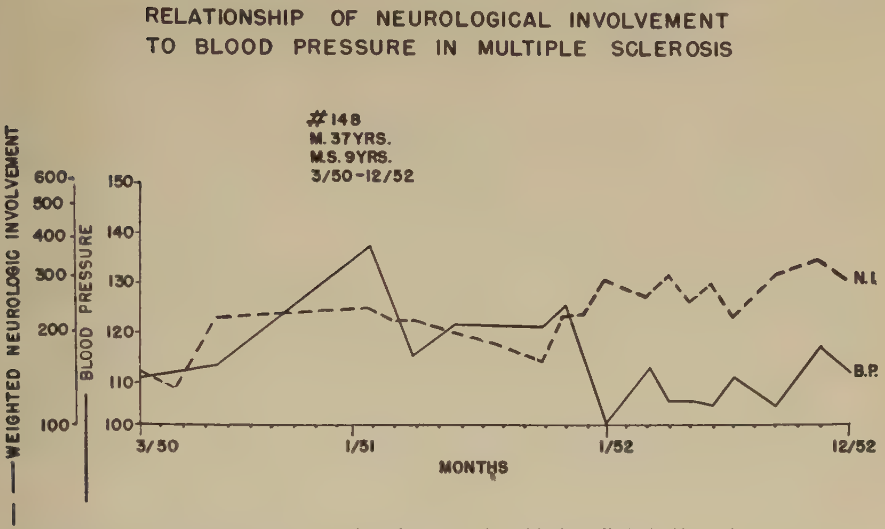

FIGURE 3. #148—WM37. Long-range clinical retrogression with clinically insignificant fluctuations accompanied by fall in blood pressure.

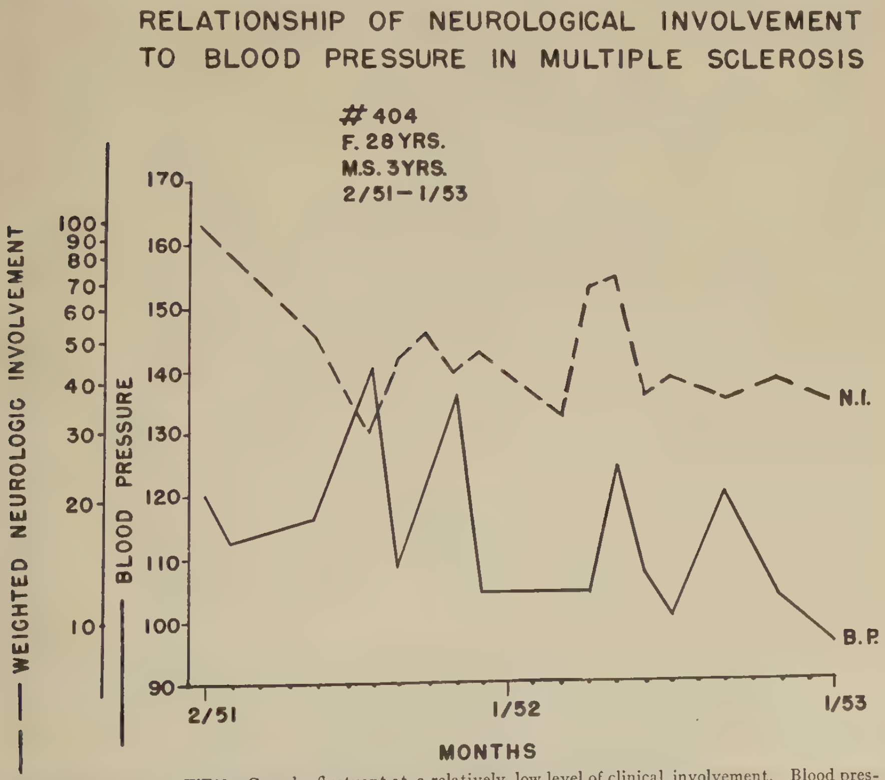

FIGURE 4. #404—WF28. Grossly fluctuant at a relatively low level of clinical involvement. Blood pressure peaks predict or accompany clinical exacerbations followed by early remission.

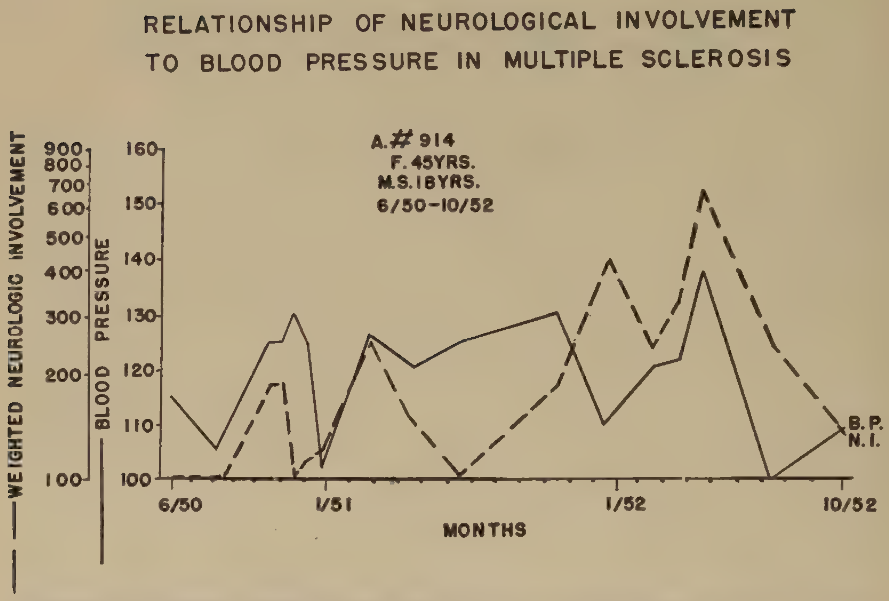

FIGURE 5. #914—WF45. Fluctuant with stationary mean—blood pressure peaks accompany significant episodes of clinical retrogression, predicting early remission.

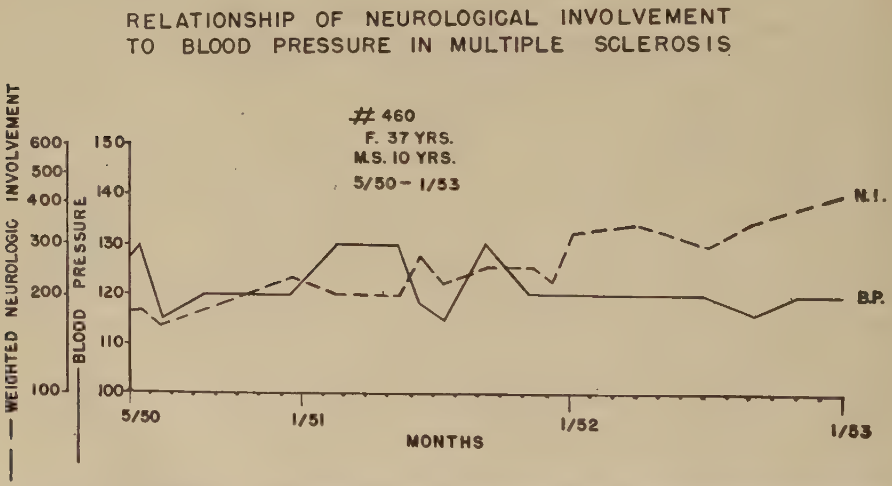

FIGURE 6. #460—WF37. Slowly progressive course in which stable blood pressure trend predicts worsening in last 18 months shown.

that few significant fluctuations may be missed, but this frequency of observation is more important for the prediction of transient fluctuations. Even when only infrequent appraisals are possible, it soon becomes possible to visualize the probable progress of a case for a number of months in advance. The case represented by a curve showing little fluctuation may be expected to continue the

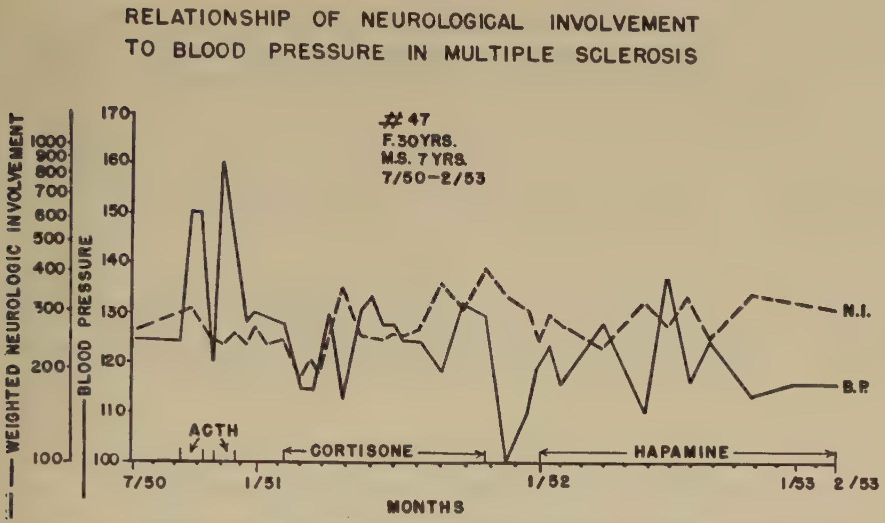

FIGURE 7. #47—WF30. Slowly progressive with fluctuation. Blood pressure relationship is predictive and mirrors curve of neurological involvement except where apparently showing marked effect of adrenocorticotrophic hormone.

observed trend for long periods of time, and the extrapolation of points following this trend will closely approach the level observed later.

This preliminary report is made with full knowledge of certain defects in the method described, some of which may be corrected as further observations make mathematical formulations possible. Other defects, which probably derive from unknown features of the disease itself, will be explained as our knowledge increases. The material is not completely representative, in that most patients seen have been ambulatory; observation has usually begun well after onset and diagnosis. We therefore have little information on the question of whether observation of very early or severely disabled patients would consistently show findings similar to these we report. Some cases characterized by marked lability of blood pressure may not show the usual relationship of the curves.

On the other hand, use of the method has established for us a graphic representation of patient status which is derived from the objective report of a neurological examination. The numerical value assigned accurately indicates the clinical status of the patient at the time of examination and, by its charted position relative to previous examinations, it shows the degree of fluctuation experienced from time to time. A curve constructed from these values clearly shows the picture of progression, stationary status, or remission. If blood pressure recordings are plotted along with the examination findings, there is a relationship of the two curves that furnishes an index of remittent or progressive changes which may be expected to take place within a short time. Duplication of these findings in any patient is easily accomplished by different examiners, or comparable reports of separated groups of patients may be prepared, making it possible to compare clinical progress on the basis of total neurological involvement, thus eliminating the use of criteria depending on changes in arbitrarily designated symptoms or signs and the error of subjective reports.

After adequate periods of observation, a type curve is established for each patient which serves well as a control for future observation. A consistency of course for the individual case of multiple sclerosis has been a basic observation mentioned by many clinicians.[4] Such a procedure serves to establish a practical value for the curve developed by the method described, namely, a positive scale of reference which serves as a control for evaluation of the efficacy of any treatment routine.

If disability of whatever type or degree has been established for one year or more, it has been observed that major improvement does not take place. The best criterion of success for a therapeutic routine is the maintenance of a stationary status or the prevention of progression at the rate expected for the individual case.

Summary

When systolic blood pressure readings and neurological examination values for multiple sclerosis patients are charted in parallel, the curves produced show a remarkable tendency to assume relationships which are typical for the clinical course later observed in each case. The visual impression of a trend marked by fluctuation of varying degree is immediately apparent in cases observed for 12 to 18 months, and shorter periods furnish seemingly reliable indices of future developments. Rather frequent observations are essential. A discussion of the observed correlations as they bear on the time and severity of fluctuation and remission, as well as some sources of error which must be kept in mind, leaves the impression that a procedure has been devised which will enable the clinician to predict with some accuracy the course which a case of multiple sclerosis will follow. Marked departure from the expected relationship of the curves or their trends may warrant the assumption that a major deleterious or beneficent external factor has become operative. It is suggested that there is value for better comparison of the results of treatment when using a quantitative report of patient status, which in large degree eliminates uncertainties of definition for remissions and exacerbations, and the errors of undue emphasis on minor fluctuations or purely psychogenic variation of symptoms.

Conclusion

Whenever the blood pressure rises spontaneously before and/or during an attack of multiple sclerosis, prognosis for recovery from this attack is good; when, however, the blood pressure remains unchanged or falls during the attack, the probability that the attack will result in a permanent deterioration of the disability status of the patient is high.

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EPIDEMIOLOGIC FACTORS IN THE ETIOLOGY AND PROGNOSIS OF MULTIPLE SCLEROSIS*

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Introduction

The purpose of this paper is to examine some of the applications of the epidemiological method to multiple sclerosis.

The epidemiological approach, through field and statistical study, evaluates disease as it occurs under natural conditions in groups of people and compares features of both the sick and well populations. More specifically, the epidemiologist attempts to measure "the frequency and kind of disease manifested by different fractions of the population, from such simple divisions as those of age, race, and sex to the more complicated separations by occupation, social status, economic situation, *etc.*, all in terms of the time and place that the disease occurs."[1] The proper analysis of epidemiological data in the light of clinical knowledge or laboratory testing may reveal relationships of the affected individuals to their social or biological environment which may have resulted in the onset and progression of the disorder.

The epidemiological approach may be considered as one of the three general methods by which we develop knowledge of disease, the others being the clinical study of the individual patient and the experimental approach in the laboratory. "No single one of these suffices to the exclusion of the others; each has its individual usefulness, and the fullest measure of progress is to be expected when all are brought into action."[1] Indeed, we can expect that even slight progress in one field will potentialize progress in the others.

This report is based largely on the results of recently completed studies sponsored by the National Multiple Sclerosis Society in cooperation with the Public Health Service and the Canadian Ministry of Health and Welfare. Where these data are insufficient to answer some pertinent questions, they will be supplemented by reports of others whose investigations were directed in a more specific vein.

An essential preceding step to an effective use of the epidemiological method in field studies is the clear description of the clinical syndrome and, if possible, the definition of the disease entities which represent the syndrome's component parts. Ideally, a case of the disease entity represents the unit in the epidemiological counting system. Unfortunately, in multiple sclerosis, we have no assurance that what we count as cases are the same disease entity, nor do we have any specific laboratory or clinical aid to diagnose early or atypical cases. Furthermore, the relatively low incidence of the disease adds tremendously to the effort of obtaining representative samples of cases in defined geographic areas. In spite of these difficulties, many other investigators have conducted epidemiological surveys of multiple sclerosis, and have reported variations in

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* The epidemiological investigations by the authors were supported by grants from the National Multiple Sclerosis Society and the Canadian Ministry of Health and Welfare.

the prevalence of multiple sclerosis with geographic location. They have also reported conflicting results in the study of racial susceptibility, occupation, *etc.* In no case, has any previous study of morbidity and mortality been conducted in a uniform manner over an extensive geographic latitude.

In the belief that more accurate statistics might eliminate some of the confusion in this field, the Statistical Committee of the National Multiple Sclerosis Society, under the chairmanship of Doctor L. C. Kolb, Jr., then with the Public Health Service, proposed, in 1947, that an investigation be undertaken "to determine the extent of multiple sclerosis and to study the influence of climate and race on its distribution."

Consequently, as our studies developed, we found that we had set out to do the following:

(1) To map the mortality distribution over a wide geographic area where similar mortality coding and classification systems would provide the most comparable data.

(2) To determine the morbidity and mortality in several widely separated large communities in which the standards of medical practice were high. These studies have been completed in Boston, Winnipeg, New Orleans, Denver, and San Francisco.

(3) To study life expectancy and to determine whether it differed geographically.

The next step was dependent on our confirming the clinical impression that there is less multiple sclerosis in the southern part of the United States than in the northern part and in Canada. When this impression had been confirmed, we attempted:

(4) To compare the clinical characteristics of the disease in the two communities, *viz.*, New Orleans and Winnipeg, whose latitude and multiple sclerosis prevalence differed the most, and

(5) To study in as broad a range as possible the characteristics of the diseased individuals in order to elucidate any etiological or associated factors. We therefore compared numerous characteristics of our Winnipeg patients and their environment prior to the onset of the disease with a representative sample of the Winnipeg population.

The last step of our program called for the specific testing by appropriate techniques or devices any promising lead suggested by the differences in the patient and control groups which would be consistent with the findings of the geographic investigations. It will soon be clear, we believe, why this last and crucial step has not been initiated.

METHODS AND FINDINGS

As the details of the methods employed in these studies have been described elsewhere, we shall merely summarize them as we present the principal and a few incidental findings.

I. Mortality Distribution and Mortality Trends in the United States and Canada

The age-adjusted mortality rates for the United States by regions and for Canada in 1947 have been published elsewhere.[2] The northern regions of the

United States and Canada had rates that were two to three times higher than that of the South.

In an earlier report,[3] one of us attempted to answer the question of whether multiple sclerosis was becoming more frequent. After reviewing the available statistics, the author agreed with Steiner,[4] who had previously stated that there was "an increasing incidence of the disease in various countries but this is apparently due to more widespread knowledge of its clinical appearance."

Mortality statistics for a disease having as long an average duration as multiple sclerosis, unfortunately, do not provide reliable short term trends, because of the numerous factors which influence statistics. The patients dying this year represent, on an average, those afflicted two decades earlier. Furthermore, there are changes in the mortality coding system almost every ten years. In 1949, a change was made in death certificates, listing multiple causes of death, whereby the physician, rather than an arbitrary set of rules, determined the primary or underlying cause of death. This change has had the effect of lowering the number of deaths listed in the multiple sclerosis category by about 8 per cent, so that the number of deaths listed for 1949 would have been even higher if the coding system used in 1947 had been employed in 1949. Next, the National Office of Vital Statistics of the United States has eliminated all "cerebral sclerosis" death certificates from the multiple sclerosis category, since it found that these deaths, which accounted for 20 per cent of the total in the category, were not attributed to multiple sclerosis. (This correction has not yet been adopted by the Canadian Bureau of Vital Statistics and means that future rates in the two countries will not be directly comparable.) Next, the physicians' training may change with time, and this alteration may influence the concept of multiple sclerosis as a diagnostic possibility. Finally, chance effect can be expected to play a large part in annual variations in rates in smaller population groups.

In TABLE 1, the 1947 and 1949 deaths are compared. There were 125 more multiple sclerosis deaths reported in the United States in 1949 than in 1947. (We are uncertain whether there was an increase in the Canadian deaths as well.) For the next year (1950), however, 1278 deaths attributed to multiple sclerosis were reported in the United States, a decrease of 101 from the preceding year.

TABLE 1

1947 AND 1949 MULTIPLE SCLEROSIS MORTALITY, FOR WHITE POPULATIONS OF CANADA, TOTAL, AND THE UNITED STATES, BY REGIONS

	1947	1949
	Number of deaths (terminology-corrected)	Number of deaths (only U.S. terminology-corrected)
Canada (all provinces)	150	202*
United States (by regions)	1,254	1,379
North east	435	405
North central	525	574
West	151	185
South	143	215

* Status of cerebral sclerosis deaths is uncertain.

TABLE 2
SOME CHARACTERISTICS OF THE FIVE COMMUNITIES SELECTED FOR THE INVESTIGATION OF MULTIPLE SCLEROSIS

	New Orleans	Winnipeg	Boston	Denver	San Francisco
Population*	602,000	314,000	846,000	416,000	775,000
Nonwhite population	28 per cent	Negligible	3 per cent (estimated)	4 per cent	10 per cent
Increase in population in 10 years	16 per cent	12 per cent	6 per cent	29 per cent	22 per cent
Latitude	30°N	50°N	42°N	40°N	37°N
Altitude	5 ft.	760 ft.	21 ft.	5,280 ft.	15 ft.
Mean temperature:					
January	55°F	−3.5°F	28°F	30.6°F	50°F
July	83°F	66.2°F	72°F	72.6°F	59°F

* Population: Winnipeg, 1946 census; New Orleans, 1947 estimate; Boston, Denver, and San Francisco, 1950 census.

In 1949, the greatest relative gain occurred in the South. Since we do not yet have the 1950 mortality figures by region, we are uncertain whether the 1949 rise for the South is indicative of a change in the regional mortality distribution.

II. Morbidity Surveys in the United States and Canada

The morbidity (and mortality) surveys which were begun in 1949 have now been completed in Winnipeg, Boston, New Orleans, Denver, and San Francisco. TABLE 2 is presented for purposes of orientation and compares various features of the communities studied.

Reports of suspected and diagnosed cases and deaths for the ten years previous to 1949 were obtained in these cities from physicians, hospitals, nursing homes, and the offices of vital statistics. The surveys are believed to be complete and comparable except for the following:

(1) In Denver, morbidity data were located for only a small proportion of the deaths reported. Since death reports unaccompanied by detailed clinical data were not acceptable for mortality tabulations, the death rates in Denver appear deficient (FIGURE 1). It will be noted that the death rates by age in New Orleans are lowest, that those in Denver fluctuate more than the others with age, whereas the remaining three cities are higher and more uniform in configuration. The San Francisco rates are between those of Boston and Winnipeg on the one hand, and of New Orleans on the other.

(2) A review of each case reported was carried out in all cities except San Francisco, where some objection to this phase of the study was made by the County Medical Society. Strictly speaking, the data in San Francisco are less reliable than those of the other cities but, fortunately, the original case reports collected in San Francisco, on which our tabulations are based, were superior to those prior to the case review in the other cities.

The results of the prevalence determinations in these cities will be compared with the results obtained by other investigators[5, 6] in Rochester, Minn., and Kingston, Ont., whose case-finding methods were at least as thorough as those used in the larger cities. By prevalence, we mean the number of cases living (in the city) on a particular date.

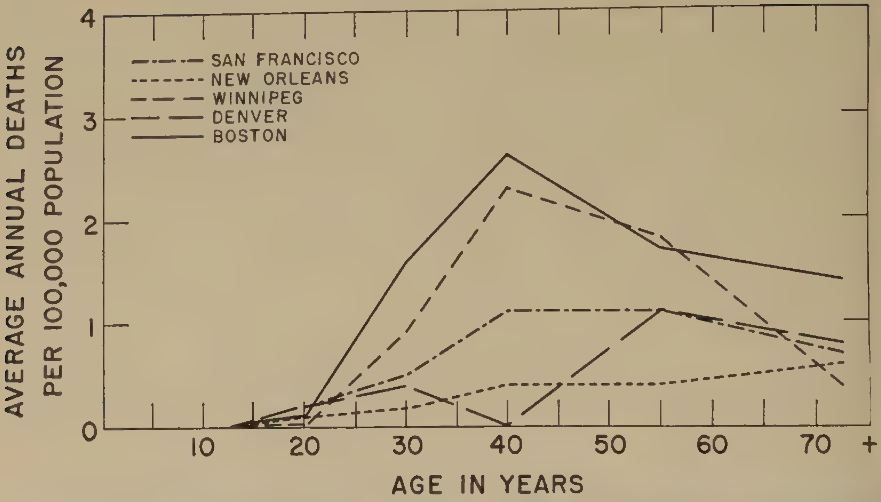

FIGURE 1. Average annual multiple sclerosis death rates per 100,000 population, by age, for deaths among "probable" cases, for the total population in Winnipeg, Boston, Denver, San Francisco, and New Orleans, 1939 to 1948.

TABLE 3

MULTIPLE SCLEROSIS PREVALENCE RATIOS* IN SELECTED COMMUNITIES OF THE UNITED STATES AND CANADA

City	Total population†	Per cent nonwhite population	Prevalence ratio per 100,000 population	
			White	Nonwhite
Rochester, Minn.	33,000	<1%	64	—
Kingston, Ont.	30,000	<1%	53	—
Winnipeg, Man.	314,000	<1%	42	—
Boston, Mass.	846,000	3%	41	31
Denver, Colo.	416,000	4%	38	11
San Francisco, Calif.	775,000	10%	30	—
New Orleans, La.	602,000	28%	13	8

* Prevalence ratios: Rochester, Minn., 1948; Kingston, Ont., 1949; other cities, January 1, 1949.
† Population: Kingston, Ont., 1945 census; Winnipeg, 1946 census; New Orleans, 1947 estimate; Rochester, 1948 estimate; Boston, Denver, and San Francisco, 1950 census.

TABLE 3 shows the prevalence ratios for the white and nonwhite populations. The ratios for whites are highest in the semirural communities of Rochester, Minn. (population 33,000), and Kingston, Ont. (population 30,000), but neither of these values can be said to differ from those of Winnipeg, Boston, and Denver by a statistically significant amount. The value for San Francisco is slightly lower and that for New Orleans is lowest. Too much weight should not be given to the exact value of the ratio between the prevalences (the large northern communities being about 3.6 times that of New Orleans), since it is conceivable that the pattern of medical care varies somewhat in the cities studied and, as will be shown, the value in New Orleans is probably excessive. If we bear in mind the general features brought out in TABLE 2, these findings suggest, first, that the communities with the "northern" type of climate have the highest rates. There is insufficient evidence to indicate a difference by size of community. The fact that Denver, although intermediate in latitude, has a rate which we consider high suggests that a climatic factor rather that latitude alone is associated with the frequency. We have no method for discovering patients who have not sought medical care. If people in New Orleans tend to wait longer before consulting their doctor or hospital for a certain symptom than do people in the other communities, the reported prevalence in New Orleans would be unduly low. It seems extremely unlikely, however, that such a difference in the psychology of the population is responsible for the large differences that were observed.

The nonwhite ratios in New Orleans and Boston do not differ significantly from the white ratios in the same cities. In Denver, the ratio of 11 per 100,000 population represents two living patients among the 18,000 nonwhite population, but little reliance can be placed on this figure. The nonwhite population is so small that, by chance alone, one might reasonably expect a difference of this degree from the white ratio. Furthermore, the nonwhite population in ten years increased 112 per cent in contrast to a 27 per cent increase in the white population; so that, on an average, the nonwhite residents would not have been exposed for as long a period of time to any possible local disease-provoking factor as the "permanent" white population of the area. Also, the major gains in the nonwhite population had taken place in the age group of 24 years and under, where the chance of suffering from multiple sclerosis is not as great as in subsequent age groups.

One other pertinent factor might be mentioned since it may affect the white and nonwhite comparisons of any community in which the recent population increase for the two races differ. It is probable that much of the increase in the nonwhite population consists of persons or families in which the adults migrated to Denver primarily to obtain employment. These newer members of the community would not only have a lower average age than the populations from which they were drawn (and to which they were migrating), but they would also be expected to be healthier.

In San Francisco, the nonwhite population (particularly the Negro population) has increased at a more rapid rate than the white population. The nonwhite population, in 1940, was 4,800 Negroes and 27,000 other races, mostly Chinese. In 1950, the Negro population had increased ninefold to 43,500 and the other nonwhite populations had increased 40 per cent to 37,900, whereas the increase in the white population was merely 14 per cent.

In San Francisco, there were no living probable cases among the 80,000 nonwhite population on Jan. 1, 1949, according to our definition of a case. We are uncertain whether our study in San Francisco is as complete for the nonwhites as for the whites, but the increase of over 100 per cent in the total nonwhite population in the last ten years might have been an important factor in the small nonwhite rates. We did obtain reports on the following nonwhite patients. Two Chinese patients born in China had their onset of the disease at ages 29 and 41, while residing in San Francisco. One died in San Francisco in 1948, and the diagnosis was reported as autopsy-confirmed. We were unable to trace the other Chinese patient after 1942 and have dropped him from our tabulations. There were also three Negro cases reported, two classified as "possible" only and excluded from the tabulations, and one "probable" case which we were unable to trace after 1945.

Even if the racial differences are smaller in Boston and New Orleans, it is unlikely that the systematically greater white prevalence can be assigned to pure chance fluctuations. Possible effects of difference in the quality of medical care, however, make it necessary to conclude that we have insufficient evidence from our study to show any racial susceptibility or resistance.

It is of interest in regard to the question of racial susceptibility that one of the colored female patients in Boston, who was included in our prevalence count, died in 1949 and came to autopsy. The gross and microscopic findings were reported as typical of multiple sclerosis.

The next few figures illustrate prevalence and incidence rates by ages in the communities surveyed. They will be presented with only brief comments, as the detailed analysis will appear in a separate report.

FIGURE 2 shows average annual incidence per 100,000 population by age for both sexes in the white population. By average annual incidence, we mean the average number of new cases per year. The configuration in all cities, except Boston, shows a peak in the age group of 25 to 35 years, followed by a rapid

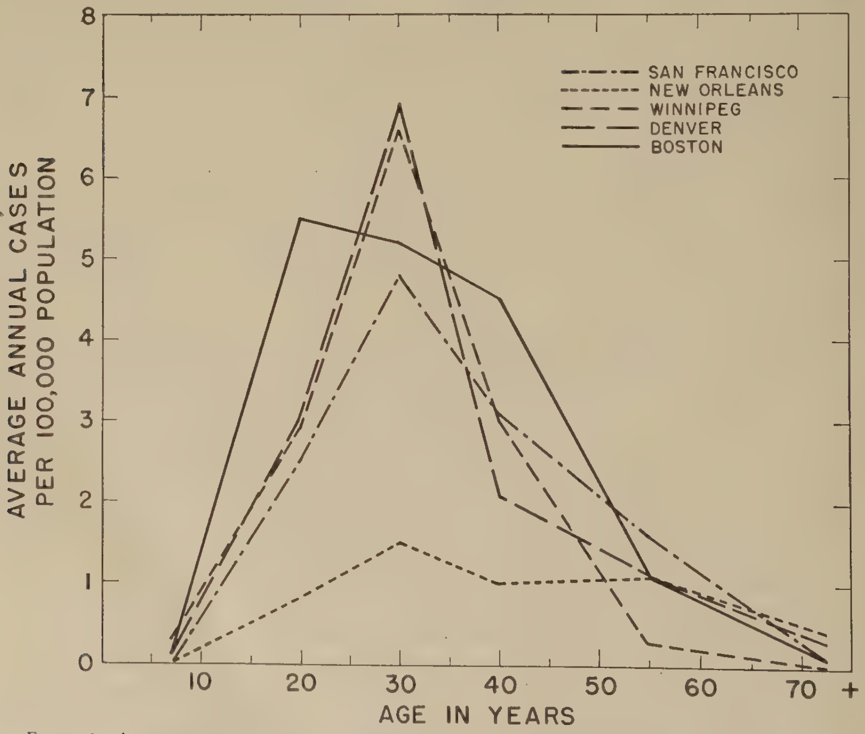

FIGURE 2. Average annual multiple sclerosis incidence rates per 100,000 population for the white population, by age, for Winnipeg, Boston, Denver, San Francisco, and New Orleans, 1939 to 1948.

TABLE 4

MEDIAN AGE AT ONSET, BY SEX, FOR 1939–1948

Community	All races	
	Male	Female
	yrs.	*yrs.*
Winnipeg	31.3	29.1
Boston	33.4	29.1
Denver	34.2	30.3
San Francisco	38.7	32.6
New Orleans	40.0	33.6
Müller (Sweden)	26.1	24.2
Limburg (composite study, both sexes)	27 yrs.	

decline, that in Boston peaking early but with almost a plateau for the 15-to-35-years-of-age group.

TABLE 4 shows the median age at onset by sex for white populations. Although the configuration of the incidence with age shown in FIGURE 2 is similar to that obtained by other investigators from direct interview of patients, our age distribution is shifted slightly toward the older age groups. The median values obtained in all cities are higher than those reported in the analysis by Limburg,[7] in which the median value was about 27 years and that of Müller,[8] in which it was about 26 years for males and 24 years for females.

Our values are uniformly higher for males than females, and several years greater than that reported by the others. This latter difference may be attributable, in part, to the fact that our data were not based on direct questioning of the patients but on hospital records and physicians' records and memories which may have been less accurate. There is one item of particular interest in this table, however: in those cities having the highest prevalence, the age at onset for both sexes is lowest, and vice versa. This finding suggests that the inciting factor not only acts to a greater degree in the cities of higher prevalence but also affects the patients earlier.

The average annual incidence rate for the cities is as given in TABLE 5. The value for New Orleans is about one third that of the other cities. The value for San Francisco is only slightly lower than that of the "northern" cities.

The configurations of prevalence ratios with age show a rather uniform type of distribution (FIGURE 3). The ratios are highest for Winnipeg and Boston. Denver is only slightly lower although shifted toward the younger age groups. San Francisco is intermediate, and New Orleans is lowest.

The ratios for each of the sexes separately (FIGURES 4 and 5) show that the general order of rates is maintained regardless of sex. It is clear, however, that ratios for females are higher than those for males in all cities.

In the next table (TABLE 6), prevalence and incidence and mortality by sex are compared. All rates with one exception are higher for females than males. Reports of others show variable sex preponderance.[8, 9, 10] Mortality statistics for the United States, however, would seem to indicate that there is no selective association whatever between multiple sclerosis and sex.[7] Furthermore, in a previous analysis[3] of the data, before those of Denver and San Francisco

TABLE 5

AVERAGE ANNUAL INCIDENCE RATE PER 100,000 POPULATION BY CITY, 1939–1948

Community	Rate per 100,000 population
Boston	2.6
Denver	2.3
Winnipeg	2.2
San Francisco	2.1
New Orleans	0.8

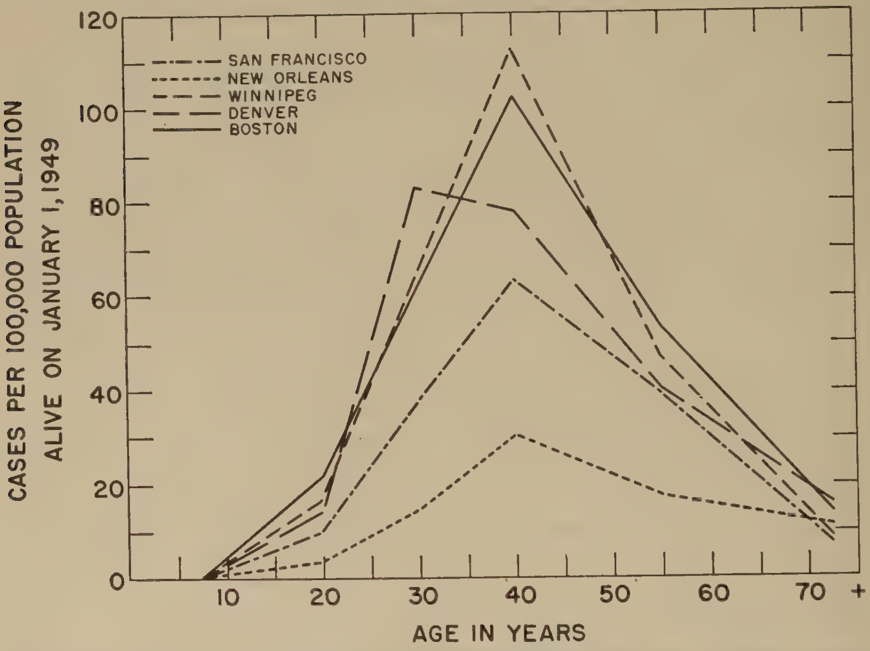

FIGURE 3. Multiple sclerosis prevalence ratios per 100,000 population (New Orleans population estimated, 1947; Winnipeg population from 1946 census; Boston, Denver, and San Francisco from 1950 census), by age, for total white population. Winnipeg, Boston, Denver, San Francisco, and New Orleans. Based on a number of probable patients known to be living in the cities on Jan. 1, 1949.

became available, it was suggested that the earlier reported onset in females, the likelihood that they would seek medical care earlier and more frequently, and the possibility of a greater proportion of misdiagnosed hysteria in females might account for the apparent increase in morbidity without a corresponding increase in mortality. In that paper, it was pointed out that if the comparisons by sex were limited to patients hospitalized (presumably those having a more severe disability) the difference by sex would disappear. The increase in the number of females appeared to be attributable to nonhospitalized cases reported by private physicians. The possibility that these factors still influence the statistics is reiterated, but we must conclude that our figures show higher female rates.

We should like to digress from our main theme for a moment to answer a

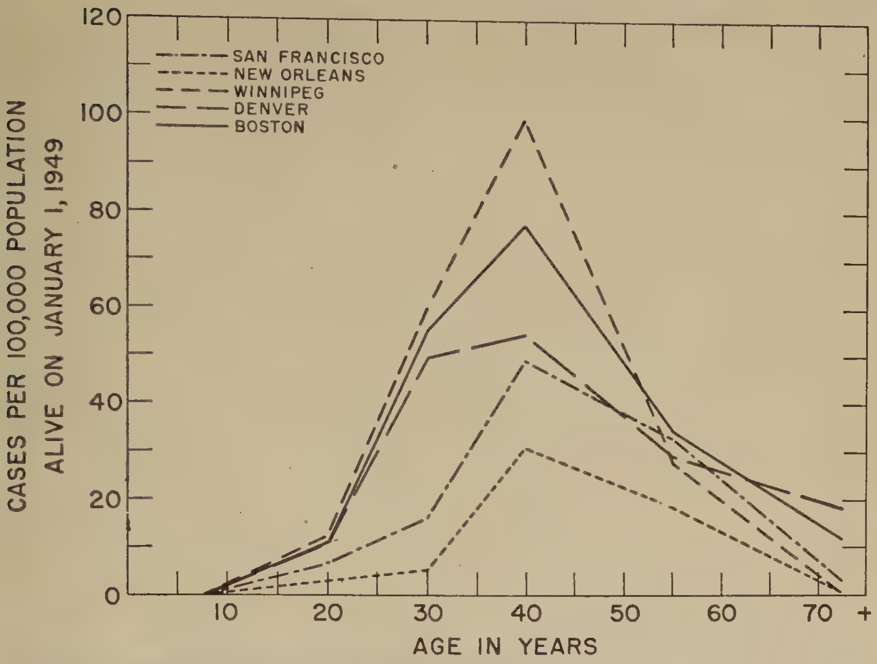

FIGURE 4. Multiple sclerosis prevalence ratios per 100,000 population, by age, for white males in Winnipeg, Boston, Denver, San Francisco, and New Orleans. Based on a number of probable patients known to be living in the cities on Jan. 1, 1949.

question which we have been asked repeatedly but which we previously avoided except in fairly precise statistical terms; *i.e.*, how many cases of multiple sclerosis are there? We believe that our prevalence, mortality, and life expectancy figures are the most accurate available for a general estimate; but our data are limited to the United States and Canada. Our estimates are also limited by our definition of a case; *i.e.*, one in which signs and symptoms of multiple sclerosis have been present at one time or another and where other diagnoses have been reasonably excluded. Our attempt to make this estimate is prompted by the following comment in a recent popular magazine article:[11] "An inevitable product of the lack of reliable current data has been the growth of a sizable body of counterfeit medical statistics—figures worked out for various purposes by organizations or individuals without the resources to gather information directly and without the sense of caution required for the numbers game." An example is "the figure of 250,000 often given for the number of multiple sclerosis cases; death data indicate that there can be, happily, no more than thirty or forty thousand cases of this paralytic disease in the country."

The bases for the values of 250,000 and 30 to 40,000 are somewhat insecure. The first is little more than an exaggerated guess. The smaller figure is probably a more accurate measure of diagnosable cases. The author, however, has used as his source of data mortality statistics alone and, in an earlier section of the same paper from which the above quotations are drawn, he had indicated how unreliable such statistics, unsupported by survey data, may be.

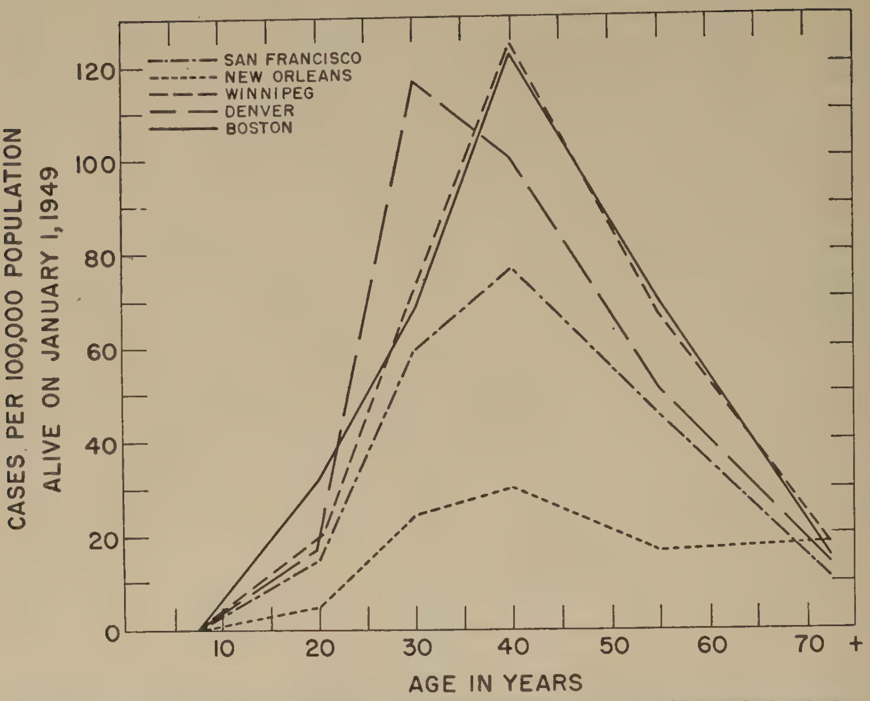

FIGURE 5. Multiple sclerosis prevalence ratios per 100,000 population, by age, for white females in Winnipeg Boston, Denver, San Francisco, and New Orleans. Based on a number of probable patients known to be living in the cities on Jan. 1, 1949.

TABLE 6

FEMALE AND MALE PREVALENCE RATIOS, AND INCIDENCE AND MORTALITY RATES PER 100,000 POPULATION; WHITE POPULATIONS ONLY, WINNIPEG, BOSTON, DENVER, SAN FRANCISCO, NEW ORLEANS; 1939–1948

Community	Prevalence ratios per 100,000 population			Incidence rates per 100,000 population			Mortality rates per 100,000 population		
	F	M	F/M	F	M	F/M	F	M	F/M
Winnipeg	50.5	32.7	(1.5)	2.68	1.76	(1.5)	0.9	1.0	(0.9)
Boston	51.6	29.9	(1.7)	3.36	1.78	(1.9)	1.3	1.0	(1.3)
Denver	49.5	26.1	(1.9)	3.1	1.3	(2.4)	0.5	0.3	(1.3)
San Francisco	38.1	21.2	(1.8)	2.6	1.5	(1.7)	0.9	0.6	(1.5)
New Orleans	14.9	10.6	(1.4)	1.01	0.53	(1.9)	0.3	0.2	(1.5)

On the basis of our survey data, we should estimate that there are, at present, about 70,000 cases in the United States and about 9,000 in Canada. These figures include cases diagnosed as well as those which are symptomatic and under medical observation but not yet diagnosed. The figures are not adjusted for that indefinite percentage who may have possibly recovered, or whose disorder is so mild that they have not sought medical treatment.

These figures are not only reasonable, they are terribly impressive, especially to those of us who recognize the tragedy of the disorder from contact with even a single patient or his family. From a public health and preventive medicine standpoint, multiple sclerosis is obviously one of the most important and challenging of our neurological problems.

III. Prognosis

(A) *Development of disability.* (*Review of literature.*) The analysis of many statements on the course of the disease shows considerable disparity. Remissions are reported as a frequent event in some series of cases and as infrequent events in others. The prognosis is reported as hopeless by some and as more promising by others. Some investigators state that certain clinical forms have a more favorable outcome, while other investigators report the opposite. Such differences are attributable not merely to the protean manifestations and the generally unpredictable course of the disease, but also to differences in the method of selection of cases, the system of classification, and the terms used to describe the improvement or progression of disability.

In the absence of a specific method of diagnosis, cases are selected by different investigators on the basis of a wide variety of clinical characteristics. MacLean and Berkson[12] included in their series only cases meeting certain diagnostic criteria whose onset occurred between the ages of 15 and 45 and which had had at least one remission. Kolb[13] and others[14, 15, 16] included other diagnostic criteria and excluded the requirements of remission or age limits. Cases from a variety of sources were often mixed indiscriminately, although Brown and Putnam[15] found that patients seen in private practice (or in an outpatient department setting) had a better prognosis than those seen in the neurological wards of a hospital. This finding might be expected, since the hospitalized patients probably have a more rapidly progressive and disabling form of the disease.

The attempts to classify various clinical forms of the disease have not been very successful. Not only are a variety of terms used but the same term may be used in different ways by different investigators. For example, Millar[17] studied the outcome of cases on the basis of whether the onset was monosymptomatic or polysymptomatic, while Thygesen[14] did the same thing but classified onsets as "acute or subacute" and "insidious." Prognostications are given for cases described as "remittent" or "chronic progressive," but since such descriptive terms can be applied only retrospectively, the distinction is of limited value in estimating the prognosis for specific cases.

As it is difficult to systematize the impressions of the different investigators who have studied prognosis, the reader is referred to another paper in which summaries of numerous reports on prognosis are presented.[18] We shall limit our review here to the question of duration of life after the onset of symptoms.

(B) *Duration of life after onset.* The average duration of life estimated from the onset of symptoms to death has usually been determined for patients who died during a limited period of study and has generally ranged from 7 to 12 years. This method of measuring duration is obviously unsatisfactory, for it is bound to give estimates which are too low. Patients in such series who are still living at the end of the study period have, on an average, a more benign course of the disease than those who died. Exclusion of the living patients results in a selection of patients having a higher mortality.

Another source of error, also tending to reduce the estimate of life expectancy, is general to all methods that do not involve the follow-up of a number of cases from their onset until death. Because the early symptoms are often vague and accompany an insidious onset, there may be a tendency on the part of the patient to forget such events and to emphasize the symptoms of a recent exacerbation. In our surveys, we found that the most advanced cases were reported with the highest age at onset. The most likely explanation of this finding seems to be that, in cases of long duration, the date of an exacerbation, rather than the date of the first symptoms, is often given as the time of onset. The magnitude of the resulting reduction in calculated life expectancy is not known, but will obviously depend on the quality of the medical history elicited at the time the patient is first seen in consultation.

There are a few series in which the average age at death for autopsy-confirmed cases is reported. These cases are, of course, selected samples and may not be representative of all who die of multiple sclerosis. Among these cases, however, the median age at death is approximately 45 years.[19, 20] This age, minus the median age at onset of 27 years as given, would result in an average duration of 18 years.

Only one study has been brought to the attention of the writers in which the history of a fairly large and representative group of patients has been followed until the majority had died. Allison in his survey of North Wales in 1929 located 40 living patients. A follow-up of all the cases in 1940[21] showed 28 patients to be dead and 12 still living. The average number of years lived after onset by the 40 patients was at that time 20 years, a figure which will have to be raised by the additional years to be lived by the 12 survivors. Since the duration at the time of establishing the prevalence in 1929, however, was already 10 years, the average duration at death in this group will not be representative of all people who get the disease. Cases having long duration will tend to be overrepresented in the material. This bias, however, is easily removed by applying a modified life table technique, where person years of observation are counted between 1929 and 1949 only. The result of such a computation will be presented in the next section.

(C) *Life expectancy as determined by life table methods.* Survival studies by life table methods have been reported by Kolb[13] and by MacLean and Berkson.[12]

Kolb divided his patients into three groups with regard to age at onset, 12 to 24 years, 25 to 34 years, 35 years and over. He reports as follows: "It was found that the risk of dying was greater for the multiple sclerotics in all three age groups than for similar age groups in the general population; and that in all three age groups the longer the disease had existed, the greater was the disparity between life expectancy of the patient and that of the general population. There was some evidence that the duration of the disease is more important than chronological age in determining the risk of dying with multiple sclerosis, since the probabilities of dying for the multiple sclerotics in the three age groups were closer than they were for the various age groups of the population as a whole. . . . The conclusion may be reached that, although the risk of dying is slightly greater for the multiple sclerotic than for the general population, these patients do have a life expectancy greater than is commonly believed. It is expected, with the greater ability to treat the acute infectious disorders within the general population as a whole, that the life expectancy of the multiple sclerotic will increase as does that of the other members of the population."

MacLean and Berkson[12] determined the survival and disability rates for 418 patients seen at the Mayo Clinic from 1934 through 1939. Only cases which had shown one or more remissions were accepted, and the average duration of illness on first visit to the clinic was 7 years. The results are, therefore, as the authors point out, not representative of all patients having the disease, but purports to serve as a base line for judgment of results obtained with the use of therapeutic measures. The five-year survival rate for the multiple sclerosis group was found to be 95 per cent of the normal population survival rate, and the ten-year rate was 85 per cent of the corresponding normal rate. For those patients who had survived to Jan. 1, 1950, and who had been able to walk and work at the time of the first clinic visit, about two thirds were still able to walk and work after five years. After 10 years, about 40 per cent were still walking and working.

The difference in frequency and age at onset between the northern and southern communities in North America was described earlier in this paper. This finding suggests that the causative factor or factors of the disease are more prevalent in the northern communities or that some important causative factor present in the northern communities is absent in the South. If exacerbations of the disease were caused by repeated exposure to an external agent, such exacerbations might be expected to be more frequent in the northern communities. Consequently, life expectancy of the northern patients would be expected to be shorter than that of the southern patients. If life expectancy were the same, it would suggest that exacerbations and remissions occurred to the same extent and were due to some endogenous mechanism.

The life expectancy based on the reports collected in the community-wide surveys in Winnipeg, Boston, and New Orleans was determined by life table methods. The results in TABLE 7 are summarized, together with the results of the same procedure applied to Allison's material from North Wales. Owing to the small size of the materials, the expectancies for New Orleans and North Wales are given for the sexes combined only.

The average life expectancy after onset of symptoms is about 21 years. The agreement between the various areas is very good, but certain limitations of the material must be pointed out. Allison's study has the advantage of being a long-term follow-up. The material in the other three areas was collected by a method which was essentially retrospective in nature and is therefore more open to bias. Secondly, the New Orleans material is not only small, but the diagnosis in many living patients is not acceptable, according to a later examination of the patients to be described. Since no correction could be made in the diagnosis of deceased patients, it was not possible to utilize the revised diag-

TABLE 7

PERSON YEARS OF OBSERVATION AND LIFE EXPECTANCIES AFTER ONSET IN FOUR GROUPS OF MULTIPLE SCLEROSIS PATIENTS

	Boston 1939–48			Winnipeg 1939–48			New Orleans 1939–48	North Wales 1929–49 (Allison)
	Male	Female	Both sexes	Male	Female	Both sexes	Both sexes	Both sexes
Person years of observation	1108	2112	3220	424	704	1128	(514)	456
Mean life expectancy	19.0	22.8	21.5	17.3	23.4	21.2	(ca. 22.0)	20.8
Median life expectancy*	19.3	23.3	21.9	20.4	26.4	23.4	(ca. 26.0)	18.1

* Median life expectancy: the duration at which half the people who contracted the disease have died.

nosis for recalculation of the life expectancies. A similar examination of patients in Winnipeg gave a good diagnostic agreement, and one could reasonably expect the same good diagnostic agreement to hold true in the Boston area.

The results of this North-South comparison afford little help to the physician trying to decide whether or not to recommend migration to a warmer climate to his patient. The incidence of multiple sclerosis appears to be lower in the South, but there is no evidence that, once this disease having such an unpredictable course has occurred, change of residence will influence its progress. There are available many case histories of patients whose condition steadily deteriorated in spite of migration to the South, and there are cases which happened to improve after the patient migrated farther north. It would seem, however, that in the absence of specific treatment or spontaneous remissions, migration to a warm climate, as Putnam[22] has recommended, would be worth trying, but *only* if there is no severe economic or emotional hardship to the patient and *only* if the patient recognized that we are uncertain that such a move will be beneficial.

IV. Comparative study in Winnipeg and New Orleans

It was noted that the frequency of multiple sclerosis, as measured by incidence, prevalence, and mortality was much greater in the northern cities than in New Orleans. Consequently, further studies of the patients in Winnipeg and New Orleans were made. These two cities were selected because, among the communities we surveyed, they are separated by the greatest latitude, their multiple sclerosis prevalence differed most markedly, and the case load in each city was within the scope of the limited time available for the studies. Since the method of study and the detailed results are presented elsewhere,[23] the principal findings are summarized here.

Most of the patients in the registry had been discovered in the community-wide surveys discussed previously, but several new cases were also found during the present study. Most of the patients in New Orleans and Winnipeg were interviewed in their homes and later examined by a local neurologist. Eightynine per cent of the previously classified "probable" patients who were examined in Winnipeg were found to be acceptable cases by the neurologists, whereas only 52 per cent of the corresponding New Orleans patients were acceptable. A more accurate estimate of prevalence ratios per 100,000 population for the two cities accordingly leaves that for Winnipeg essentially unchanged (42 in previous study, 40 following neurological review) and halves that in New Orleans (12 in previous study, 6 following neurological review). Assuming the findings in these two cities are representative of their region, multiple sclerosis appears to be about six times more prevalent in the North than in the South.

It is of interest that the large majority of the probable patients in New Orleans were born in the South and resided there prior to the onset of symptoms.

It was also found that there was a close agreement for the reported occurrence and course of various subjective symptoms in the patient groups in the two cities. There were several significant differences, however, in the abnormal findings at the neurological examination for the two groups. These differences were interpreted as more likely reflecting variations between the examining neurologists than between the examined patient groups. It was concluded that no difference could be established in the clinical picture of multiple sclerosis in Winnipeg and New Orleans, although the relative difference in prevalence was even greater than that previously reported.

V. "Controlled" study in Winnipeg

A partial explanation for the variations in prevalence noted might perhaps be found in genetic differences. Pratt *et al.*[24] have presented evidence of increased familial incidence of multiple sclerosis for which they do not consider common environment a likely explanation. On the basis of Thum's studies[25, 26] of multiple sclerosis in twins, however, it would appear that heredity in multiple sclerosis is of limited importance. One is led to suspect, therefore, that environmental factors of some kind play a part in the etiology of the disease. Actually, a large number of factors have been hypothesized from time to time; for instance, occupation, febrile illnesses, trauma, pregnancy, and nutrition. Such theories, however, have often been based on general clinical impression rather than carefully controlled observations. The usual type of "controlled" studies might be illustrated by the recent investigation of McAlpine and Compston,[27] in which these investigators compared some elements of the life history of 250 multiple sclerosis patients with that of 250 patients having various other diseases. The incidence of trauma, superficial infections, and active allergic disease for the three-month period preceding onset was reported as higher in the multiple sclerosis patients. As McAlpine and Compston point out, however, the accuracy of information concerning such factors in the two groups may not be entirely comparable. Furthermore, the control group, consisting of hospitalized patients, is quite clearly unrepresentative of the general population from which the patients came.

A few other reports might be cited. Allison,[9] in his survey, used as a control group for his multiple sclerosis patients those patients in whom the diagnosis of multiple sclerosis was rejected. He found no difference in occupation or trauma in the two groups. Müller,[8] in his comprehensive paper, rather effectively refuted the hypothesis that there is any significant connection between pregnancy and multiple sclerosis. Swank[10] noted a higher annual incidence of multiple sclerosis in the inland area of Norway than in the coastal regions. The diet of the population in the coastal regions is predominantly fish and that in the inland area is high in butter fat. On the basis of that study and other observations,[28] Swank hypothesized an association between the high intake of butter fats and the onset of multiple sclerosis. The results of such comparisons must of necessity be somewhat inconclusive, and there seemed to be need for further evaluation of the importance of various environmental factors in the etiology of multiple sclerosis. Unfortunately, the rarity of the condition makes it virtually impossible to use the ideal approach for a controlled study of a chronic disease, *i.e.*, to examine a large number of healthy individuals and follow them closely for a period of years to see what kind of persons develop the disease. In multiple sclerosis, the investigator will have to start with a group of individuals who have already developed the disease and try to appraise whatever information is obtainable on the premorbid experience of the patients.

What we intend to describe here, briefly, are the results of a study which we believe is unique in multiple sclerosis investigations in two respects. First, a patient group, believed to be representative of a large community, was compared with a representative sample of the population from the same community. Secondly, the premorbid experience of the patients, as elicited by interview, was compared with the experience of the controls prior to "onset," the "onset" years being chosen so as to match the onset years of the patients as closely as possible. The patient group consisted of the 112 patients in Winnipeg, who were classified as "probable," following the neurological examination in the survey reported in the preceding section. The 123 control individuals were selected from the families included in the Canadian Sickness Survey sample in Winnipeg. The complexities of collecting and interpreting data for such a comparison are described in the original detailed paper.[29] Only a few of the more interesting results of some of the comparisons will be summarized here.

No statistically significant difference was found in the comparison of the patient and the control groups for the following items: (1) areas of Europe from which the individuals or their ancestors had migrated; (2) place of birth; (3) education; (4) occupation; (5) residence on a farm; (6) using well water; (7) exposure to animals; (8) vaccinations and inoculations received prior to "onset" date; (9) previous illnesses; (10) head injuries causing unconsciousness; and (11) birth order in the family. The only difference not readily explainable through chance or through bias in the interview technique was an increase in the number of operations under general anesthesia for the multiple sclerosis patients prior to onset. Even this difference was not great and is considered of questionable importance. It is of interest that less butter consumption was reported by the patients than by the controls. It was obviously very difficult, however, to examine for this food item, and the possibility of bias in the interview technique could not be excluded. At any rate, no evidence to support Swank's hypothesis[28] as described earlier was found.

"The failure to bring out any clear-cut peculiarities of the patient group does not mean, of course, that multiple sclerosis patients are identical with the general population with respect to the items examined. Even in view of the admitted defects of the interview technique and the limited size of the samples, however, one can probably conclude that the 'true' difference is not great enough for any single item to be of consequence for prevention and treatment. Either the etiological factors in multiple sclerosis in Winnipeg have been missed in this study or no one of the factors studied can be responsible for more than a small proportion of the cases."[29]

The epidemiological approach with its emphasis on the relationship of the host to his environment does not necessarily mean that we have satisfied ourselves that no genetic factor was involved. Admittedly, our knowledge of the published reports prior to the recent one of Pratt *et al.*[24] made us highly skeptical that heredity was a factor of any importance. In our own studies, we found no reason to suspect genetic factors for we were aware of no more than one or two cases in any of our cities in which a close relative was also known to have the disease. Unfortunately, we did not inquire deeply into this matter nor did we determine if the extent of consanguinity of parents of patients was greater than in the general population.

It is now clear, we hope, why we have not carried out the last step of our proposed investigation: namely, the testing of any promising lead indicated by the differences in the patient and control groups consistent with the findings of the geographic investigations. We have no lead sufficiently promising for specific studies. We have noted a geographic difference in the United States and Canada. We should assume that this is somehow related to climate but we cannot be sure. We do not believe we have detected any important sex, racial, economic, or social factor. Perhaps we have clarified the situation somewhat for our laboratory and clinical research colleagues by removing, in a manner which we believe is effective, a number of erroneous concepts of cause. We hope that the hypotheses of etiology to be developed by future research will account for the unusual findings in frequency and distribution which have been described in this paper.

Summary and Conclusions

The frequency of multiple sclerosis, as measured by mortality statistics, was found to be greater in Canada and the northern United States than in the South. Following intensive statistical surveys in several cities of the United States and Canada, it was found that the frequency of the disease as measured by prevalence, incidence, and mortality was greatest in Winnipeg, Boston, and Denver; slightly lower in San Francisco; and considerably lower in New Orleans.

The average age at onset was about 30 years for females and 34 years for males. These ages are several years greater than those reported in direct clinical investigations. The age at onset was lowest in the cities reporting the highest prevalence ratios, suggesting that the inciting factor (presumably associated with climate rather than latitude *per se*) not only acts to a greater degree in cities of higher prevalence but also affects the patients earlier.

We have little evidence to indicate any great urban-rural difference in the frequency of the disease, and we have no reliable evidence that the incidence rate is increasing with time.

From other data collected, it was noted that multiple sclerosis is principally a disease of young adults, perhaps occurring to a greater extent in females. Cases were found in the nonwhite races as well as in the whites. There is insufficient evidence to substantiate that it occurs to the same degree in nonwhites, although that is our impression.

The average life expectancy after onset of the illness as determined by life table techniques is estimated as 21 years, considerably longer than that reported in most clinical studies. It was found to be somewhat similar in Winnipeg, Boston, and North Wales. Although the numerical value for New Orleans is about the same as in these other areas, it is hardly justifiable to draw any conclusions regarding mechanism of the disease or the prognosis for patients living in the South.

In a subsequent study, re-evaluation of prevalence following examination of patients by a neurologist indicated that prevalence ratio was about six times higher in Winnipeg than in New Orleans. It was not possible to establish any difference in the clinical picture of the patient groups in the two cities.

In the final study of this series, information secured by interviewing the Winnipeg patients was compared with information secured from a control group of individuals representative of the general population in the same city. The comparisons revealed no important differences in numerous environmental features studied. The patients and the controls appeared similar in respect to national origin as well as to economic and social status.

Our data indicate that multiple sclerosis seems to run its course regardless of any obvious social or environmental factors.

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SPECIFIC FACTORS IN PHYSICAL REHABILITATION FOR MULTIPLE SCLEROSIS

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In treating the multiple sclerosis patient by physical therapy or rehabilitation methods, there are three important facts which must be considered:

(1) The etiology of multiple sclerosis is unknown; therefore, we cannot treat the cause. It is only the symptoms and signs which are treatable.

(2) Multiple sclerosis, in the majority of cases, is a progressive disease, and degeneration may take place faster than rehabilitation, no matter what therapy is used.

(3) Periods of remission and exacerbation occur. All too frequently a patient may have a remission, and the type of treatment being given during that period is given credit for the improvement.

What are the symptoms and signs that occur most frequently in multiple sclerosis which may be helped by physical therapy and rehabilitation? In a study of 114 cases, Sachs and Friedman found that 81.7 per cent of the patients complained of weakness and stiffness of one or more extremities and many had ataxic symptoms and spastic or ataxia gaits. There were also a large percentage of these patients who were depressed, fatigued quickly, and had pain. Physical agents such as massage, heat, water, and exercise are useful in relieving pain, relaxing spastic muscles, strengthening weak muscles, and retraining incoordinated and ataxic movements. The rehabilitation therapist has developed methods of training patients with disabilities in self-care activities, and ambulation with the aid of gadgets, braces, and crutches.

Before any type of physical therapy or rehabilitation procedures are prescribed, it is essential that the physician or the therapist evaluate the extent of the patient's physical disabilities and the functional activities of daily living he can perform in spite of his disabilities.

The two principal disabilities resulting from multiple sclerosis are the same as those resulting from most neuromuscular conditions, namely, a limitation of motion at the joints and a dysfunction of muscles owing to weakness, spasticity, ataxia, or incoordination.

The limitation of motion can be measured by a goniometer and is usually attributable to spasticity or contractures.

The muscle function can be evaluated by the standard muscle test procedures used in poliomyelitis. Muscle tests given over a period of time will give valuable information on the progress of the disease and the results from the treatment.

The third test used evaluates the patient's ability to perform the activities essential for daily living, such as dressing, meeting his toilet needs, eating, walking, and climbing. The results of this test indicate what the patient can do with his disabilities in performing activities which require movements at the joints, muscle power, and coordination. With the information obtained from the evaluation of the patient's disabilities, the physician can prescribe the type of therapy best suited to meet his needs and measure the results of treatment.

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Physical Therapy. The physical modalities which have been found most useful are massage, hydrotherapy, and exercise:

(a) *Massage.* The movements employed in massage are useful in accelerating the flow of blood in the skin, subcutaneous tissue and muscles. Massage is also useful in producing a sedative effect on the nervous system, thus relieving spasm and rigidity of the muscles.

(b) *Hydrotherapy.* Warm baths tend to produce relaxation of the muscles and relieve pain.

(c) *Exercise.* There is no form of physical therapy as useful in the treatment of multiple sclerosis patients as active and passive movements. By means of such exercises, the movements of the joints as well as the strength of muscles and coordination may be maintained and increased. Passive movements are useful in overcoming spasticity and contractures of the muscles, adhesions in the joints, and tightening of the ligaments. They prevent deformities which may interfere with use of the extremities should remissions occur. Active movements and the arts and crafts activities are used by the therapist to strengthen the muscle groups below normal to prevent atrophy from disuse and to maintain or re-establish coordination.

Rehabilitation. Teaching the patient how to live in spite of his handicaps is the most useful form of physical and mental treatment. The patient measures progress in his lower extremities in terms of walking and in the upper extremities by his ability to eat, dress, and care for his toilet activities. The best results are obtained by working with the patient instead of on him. Action absorbs anxiety. Time does not permit a discussion of all the various types of equipment and procedures necessary to meet the needs of patients with multiple sclerosis. The methods have been published by the National Multiple Sclerosis Society in a series of four monographs.

(1) *Multiple Sclerosis. Application of Rehabilitation Techniques.*[1] This monograph gives the methods for evaluating joint motion and activities of daily living. It also discusses the rehabilitation techniques for teaching activities of daily living in bed, in the wheelchair, and with braces and crutches.

(2) *A Home Program for the Care of Bed Patients.*

(3) *A Home Program for Patients Ambulating with Aids.*

(4) *A Home Program for Independently Ambulatory Patients.*

These monographs are well illustrated and describe in detail the specific factors in physical rehabilitation which have been found most useful at Bellevue Hospital and at the New York University-Bellevue Institute of Rehabilitation.

Results to be Expected. The two chief factors which seem to influence the results of the rehabilitation program are the rapidity with which the disease is progressing and the neurological manifestations. If the disease is progressing rapidly, degeneration takes place faster than rehabilitation.

In multiple sclerosis, we may find flaccidity, spasticity, athetosis, ataxia, and loss of position sense. If the patient has only one of these neurological conditions he can be helped a great deal. If, however, he has spasticity and a loss of position sense in his lower extremities, it is almost impossible for him to ambulate without assistance. When three of these conditions exist little can be expected from a rehabilitation program. When incontinence and mental symptoms are added to the neuromuscular manifestations the problem becomes more difficult and hopeless.

Though the future for multiple sclerosis patients seems hopeless at the present time, it is essential that physicians utilize all the methods available to help these unfortunate young people. If we, as physicians, do not try every means possible to help them, we can expect them to seek help from other sources.

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OBSERVATIONS ON PHARMACOLOGICAL AGENTS RECENTLY SUGGESTED FOR MULTIPLE SCLEROSIS

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The difficulties inherent in evaluating scientifically the results of any treatment regime for patients afflicted by multiple sclerosis are well recognized.[1-5] The problems of ascertaining the correct diagnosis, the unpredictability of the natural course of the illness, the occurrence of prolonged periods of remission, the lack of universal agreement pertaining to suitable criteria signifying improvement or cure are only some of the factors complicating the picture. Many of these aspects have been discussed in this symposium. Controlled evaluations are admittedly difficult. The usual methods have consisted of (1) counting the number of and frequency of remissions and exacerbations of the multiple sclerotic in a group before, during, and after treatment, and (2) using the patient's past performance as a control for the effects of treatment. The number and frequency of attacks and remissions are estimated from the patient's history, supplemented by other physicians' records and reports of previous hospitalization. These methods, however, are not unequivocally reliable.

Nathanson[5] has pointed out how variable the disease can be in two control groups of the same size. Müller's[6] extensive study of the natural course of multiple sclerosis has shown that the activity of the disease, as measured by the number of exacerbations, varies with its duration. During the first five years, the average number or frequency of exacerbations exceeds the number to be expected later in the disease. These observations indicate the necessity for caution in judging the effects of any therapy on the course of multiple sclerosis.

It has been suggested that therapy may be evaluated by its influence on the "deterioration rate." Studies by MacLean and associates[7] have shown that in their group of 36 patients who had multiple sclerosis of the type that demonstrates exacerbations and remissions, approximately 4 per cent appear to become disabled each year in terms of walking or working. Since their series is small, the statistical validity of this figure is questionable. Extending their studies to 418 cases, MacLean and Berkson[8] found that this figure of 4 per cent is only an approximation. They believe that a five year appraisal is the minimal time period necessary to deduce reliable conclusions in the evaluation of any therapy.

Recently Brickner[9] has stressed specific criteria to be used in evaluating the therapeutic effect of rapidly acting drugs on multiple sclerosis which will control the problem of spontaneous remissions. He suggests that: (1) reversible symptoms be used as yardsticks; (2) immediacy of effect is the critical factor; (3) there must be a predictable repetition of effect. Apparently, however, only in his studies have these criteria been rigidly applied.

Alexander[10] has ascribed a numerical value to his patients having multiple sclerosis depending upon the patients' underlying neurological status, which he feels is useful in following the progress of the patient. Although this procedure has proved to be useful in his hands, it has not altered the fundamental nature of the problems, *i.e.*, in what specific manner the treatment influences the course of the illness.

Recognizing this problem, greater attention has recently been devoted to the development of specific laboratory procedures which will serve not only as a diagnostic aid but which, it is hoped, can be correlated with the relative activity of the process. When this end is attained, we shall be able to evaluate treatment scientifically.

There have periodically been many critical and comprehensive reviews of therapies used in multiple sclerosis.[1-3] Probably the most recent is that of Schumacher,[4] who in 1950 summarized his review of the status of drug treatment of multiple sclerosis by saying "... the outlook for cure of the disease by use of drugs is unpromising and that the outlook for symptomatic relief by drugs would seem in many instances to be unwarranted." Many clinicians have interpreted this conclusion as advocating therapeutic nihilism. Others have contended that this statement merely represents an appraisal of our present status of therapy applied with scientific exactness, but does not imply that the patient having multiple sclerosis should not be treated. Despite these differences in attitude within the medical profession itself, the patient and his family, not unnaturally, have increasingly pressured the physician for "treatment," and there is now less of a tendency to view as "forgotten patients"[11] those incapacitated by multiple sclerosis. Increasing application of the modern techniques of rehabilitation are responsible to a great extent for this changing attitude,[12-14] and they have primarily been directed toward improvement of the established symptoms. Extensive clinical efforts have continued, however, to be directed toward the amelioration of the underlying pathogenic process, as well as toward the modification of many of the symptoms. As was to be anticipated, a large number of the more recently available pharmacological agents have been utilized for therapeutic purposes. This paper is an attempt to evaluate the use of some of them, especially those studied since Schumacher's critical review in 1950.

Schumacher has divided the therapeutic drugs used in the treatment of multiple sclerosis into two main categories: (1) those directed toward preventing the development of lesions in the nervous system, *i.e.*, dealing directly with pathogenesis of the disease; and (2) those directed toward modifying the dysfunctions that result from nervous system defects in the patient, *i.e.*, symptomatic remedies. This seems to be a useful classification, and it will be followed in this presentation.

Drugs Aimed at Prevention (or Improvement) of Lesions

Steroid therapy. Cortisone and ACTH.—Following the initial therapeutic triumphs of cortisone and ACTH, these substances were given to many patients suffering from various neurological disorders, including many having multiple sclerosis. Although a number of investigators have undoubtedly tried these steroids in the case of patients afflicted by multiple sclerosis, reports of their clinical trial are few.

Preliminary reports[16-18] have indicated that ACTH and cortisone are of questionable value in the treatment of multiple sclerosis, and the report contributed by Merritt and Glaser to this symposium if of significance.

Glaser and Merritt[19] have previously reported the effects of corticotropin (ACTH) and cortisone on a series of 33 patients having multiple sclerosis. Approximately one third of their patients showed significant improvement of existing symptoms and signs, primarily of spasticity, ataxia, and bladder dysfunction. Sensory and chronic visual deficits were not affected. In most instances, these changes were transient, appearing only during the course of treatment and regressing afterward or during periods of placebo administration. In only two patients did improvements suggest an induced remission. These investigators concluded, "It cannot be stated at the present time that corticotropin and cortisone are suitable therapeutic agents in multiple sclerosis."

Vasodilators and drugs aimed at modifying allergic states. Histamine.—Originally introduced in the treatment of multiple sclerosis in 1944 by Horton[19] *et al.*, histamine continues to be extensively used, whether the rationale is based on the concept of allergy desensitization or as a vasodilator.

Jonez[21-23] has reported his experiences in the treatment of 1500 patients having multiple sclerosis and continues to be enthusiastic about the effects of histamine. He administers histamine intravenously, subcutaneously, by iontophoresis and repository intramuscular injection, and supplements this treatment with d-tubocurarine, vitamin B_{12}, and an allergy management, as well as physio- and psychotherapy. He stresses that this treatment regime does not cure but merely arrests symptoms, and feels that the exacerbations of the disease were reduced in number and the remissions lengthened. He advocates continuation of some form of histamine therapy for the remainder of the patient's life. He believes that the earlier the treatment is started, the more successful it is. In chronic cases, he feels that varying degrees of improvement occur and continue as long as the patient continues treatment. As yet, however, no statistical evaluation of his results is available, nor has he clearly defined an attempt to control the problems of spontaneous remissions in his evaluation.

Other vasodilators. Brickner[9] has renewed his investigations of the usefulness of rapidly acting vasodilator drugs. His orientation now is directed at studying the immediate effects on apparently reversible new symptoms. He reports having made 32 observations of rapid reversibility in 9 of 11 patients studied. The standards he has utilized in attempting to control the problem of spontaneous remissions have been discussed earlier. He stresses that the specific drug is not important but rather the ability to produce vasodilatation is the prime consideration He has found histamine, amyl nitrate, papaverine hydrochloride, nicotinic acid, benzazoline, and tetra ethylammonium chloride equally effective. He believes that anticoagulation measures should be instituted the moment activity of the disease appears, and should be maintained as long as vasodilation treatment is continued. He warns, however, that, at least in advanced cases, vasodilation therapy may not be without danger. Encouraging as his results are, and notwithstanding the fact that he has accumulated from his previous studies and from a review of the literature 102 similar observations in 25 other cases, final evaluations as to the therapeutic efficacy of vasodilation must await further confirmation and observation of the patients' course over an extended period.

Sympatholytic and adrenolytic compounds. Tetraethylammonium chloride (Etamon chloride^R)—Williams, Karnosh, and Tucker[24] have analyzed the effects of tetraethylammonium chloride given intramuscularly in 222 patients afflicted by multiple sclerosis in dosage of 350 to 1800 mgm. six times weekly. These investigators are no longer optimistic over its use and conclude that the drug appears to be only a palliative treatment, particularly in the acute phase of the disease. They believe that only moderate or no improvement can be hoped for from its use in the chronic stage. They state, however, that if it is given in the early phase of an exacerbation it is possible that the drug may prevent the formation of new "scars" in the central nervous system.

Arkin, Sherman, and Weinberg[25] treated a group of 42 patients having multiple sclerosis intensively with tetraethylammonium chloride for three weeks. Although there was slight subjective improvement, it was concluded that the drug had no influence on the course of multiple sclerosis.

Circulatory stimulants. Scheinker[26] has continued to utilize various vasopressor drugs in the treatment of multiple sclerosis in order to elevate the arterial blood pressure and to stimulate blood circulation for the purpose of counteracting "vasoparalytic vascular phenomena." He has reported the results of his observations earlier in this symposium. Final critical evaluation of the results of his therapy must await confirmation by other investigators.

Vitamins. The vitamin adjuvants continue as the therapeutic agents most commonly used in the treatment of multiple sclerosis. In view of the beneficial effects of vitamin B_{12} in pernicious anemia, it has been given, not unnaturally, to patients having multiple sclerosis.

Simson, Herfort, Krim, and Meyer[27] treated 4 patients who had had multiple sclerosis for several years, giving each 1050 μg. of vitamin B_{12} intramuscularly, daily for five months. They noted no signs of improvement.

Booth, Lawyer, and von Storch[28] studied 24 patients who received as much as 1000 μg. every other day for protracted periods. Although approximately one fourth of the patients observed an increase in appetite and a sense of well-being, there was no objective evidence of neurological improvement, aside from such fluctuations as might be expected in the natural course of the disorder. The investigators conclude that vitamin B_{12} is not effective in the treatment of multiple sclerosis.

Unpublished observations by Marks, Rusk, and Benton[29] confirm the ineffectiveness of vitamin B_{12}, even when it was given in 1000 mgm. doses daily and continued for six weeks or more. With the theoretic rationale of possibly altering the blood brain barrier and thereby rendering the vitamin B_{12} more readily available to the central nervous system, these investigators administered cortisone in doses of 100 mgm. daily for a three-week period to a small number of their patients receiving 1000 μg. of vitamin B_{12} daily. They observed no significant neurological change, although several of the patients reported subjective improvement.

Piromen^R. Piromen is a polysaccharide complex derived from various bacteria, most commonly a *Pseudomonas* species, about which there has been a great deal of publicity. Upon the demonstration by Windle and his coworkers[30-35] that Piromen was capable, in an experimental animal having a transected spinal cord, of inhibiting to some extent the glial and connective tissue scar formation and, concurrently, apparently stimulating axone regeneration across the deficit, the drug was utilized experimentally in a number of clinical neurologic disorders.

Piszczek,[36] who has administered Piromen to a large number of patients having multiple sclerosis in subfebrile dosage, usually of two or three gamma twice daily, has stressed that the best results are obtained when the patient is mobilized into an activity program. Unfortunately, his observations have not been reported except in a semiconfidential manner and through correspondence, and therefore a critical evaluation of his methods must await formal publication of his results. He acknowledges that he is not neurologically trained, and his evaluation of results appears to be based in many instances on the subjective statements of patients, rather than on the findings of the neurological reexaminations.

Bailey's[37] results with Piromen have not been nearly as encouraging. I followed an essentially similar program to that advocated by Piszczek in five patients, and observed no significant change in their neurological status.[38]

Miscellaneous agents. Recognizing the importance of the succinates in cellular respiration as well as in many other basic metabolic activities, Aird[39] administered *sodium succinate* intravenously to 10 patients, and orally, over prolonged periods, to 22 patients afflicted by multiple sclerosis. Subjective improvement was reported in 80 per cent, and objective improvement was observed in approximately two thirds of the patients by both methods of treatment. More prolonged follow-up of the patients treated orally suggested to him that approximately one half on them were benefited, specifically by (1) improvement in dysergnergia, ataxia, dysmetria, balance, and gait; (2) improvement in the flexor withdrawal reflex and clonus; and (3) subjective improvement in position sense and skinwriting. Deterioration of the patients' condition on discontinuance of the succinate was observed in four instances. Toxic effects were frequent but not alarming. Reviewing the notes more closely, one notes that most of the improvements recorded are listed as "slight." Unfortunately the criteria of and grading of "slight" and "moderate" improvement are not defined nor is the duration of therapy detailed. Critical evaluation must therefore await a more extensive and detailed appraisal.

Adenosine triphosphate (ATP) recently received considerable publicity in a popular magazine as a valuable therapeutic agent in multiple sclerosis. Intramuscular administration of 20 mgm. of adenosine triphosphate (ATP) or adenosine 5 monophosphate (My-B-Den^R) has been found to increase the adenosine triphosphate (ATP) of blood by as much as 5 mgm./100 ml.[40] It was suspected that this effect might be mediated through the increased formation coenzymes, flavine adenosine nucleotides, and other active compounds of adenylic acid. Shapiro[41] treated ten patients having multiple sclerosis with adenosine 5 monophosphate and water-soluble vitamins for a period of 1 to 22 months. His rationale was based on the observations of Jones *et al.*[42] to the effect that the pyruvate lactate ratio in the plasma of patients suffering from active multiple sclerosis is abnormal, and that the reaction lactate pyruvate requires coenzyme 1 as a cofactor. One patient had no change in status in two months. Two patients had no significant change in nine patient months. One patient had a moderate but not very helpful improvement in 10 months. Five patients had marked to moderate improvement in 60 patient months (6 to 22 months). Improvement was noted within three days to six weeks in the patients who responded. In the 10 patients treated for 82 patient months, no signs or symptoms of new neurological lesions were observed. Shapiro cautions that these observations, although encouraging, do not yet warrant general therapeutic use of adenosine 5 phosphate and water soluble vitamins in patients having multiple sclerosis and that further observations are necessary. His report in this conference has been eagerly awaited.

From personal experiences[38] with the use of adenosine 5 monophosphate (My-B-Den^{R}), I have not found that it alters the neurological status of any of my chronic multiple sclerosis patients, although several have volunteered the information that, subjectively, while on the medication, they have experienced a lessened sense of fatigue.

A *coenzyme concentrate* produced by Armour containing 7 per cent triphosphopyridinenucleotide (TPN), plus quantities of diphosphopyridinenucleotide (DPN), coenzyme A and various other vitamin B complex synthetic factors, was given parenterally by Marks and Greene[43] in 50 mgm. daily dosage to a small number of chronic multiple sclerosis patients for 14 days without effecting any change in the patients' clinical status.

Wilder[44] has been conducting studies with Pancorphen, an agent prepared by the addition of phenol to Hartley broth. By giving his multiple sclerosis patients a series of injections he claims to have brought about evidence of remissions in 30 to 40 per cent within a two-month period. A critical evaluation of his methods must, however, be deferred pending publication of the details of his management and of the criteria upon which he bases the improvement described.

As experience in the treatment of intravascular clots with intravenous trypsin accumulated, it was to be anticipated that this drug would be tried in multiple sclerosis, especialy since many investigators have postulated that the pathology involved represents the sequelae of scattered venular thrombosis in the central nervous system. Innerfield,[45] the pioneer in this form of therapy, treated several multiple sclerotics with intravenous trypsin, but soon abandoned this study. No other report of its use in multiple sclerosis is now available.

With the advent of time, the opportunity exists of scientifically disproving the efficacy of some of our earlier forms of therapy. Millar[46] has evaluated the use of arsenicals in 91 cases of multiple sclerosis who had been diagnosed at least ten years previously. Ten patients had been treated with more than three courses of intravenous arsenicals (neoarsphenamine or silver salvarsan), a total of from 24 to 128 injections each. Comparing their condition with that of ten control patients of similar age and type of disease, who had had little or no treatment (0 to 15 injections) revealed no difference in the functional capacities between the two groups.

Drugs aimed at symptomatic relief and drugs claimed to alleviate muscle spasticity. Mephenesin.—Libet and Rubin[47] report their observations on the use of mephenesin in the treatment of spasticity in multiple sclerosis. In 20 of 26 spastic patients given the elixir, slight to moderate temporary reduction in spasticity was observed, lasting from 30 to 60 minutes. They believe that the elixir, given at the time of the physical therapy hour, supplemented by tablets as a maintenance dose during the day, seemed useful in the treatment of spasticity in 10 patients. They conclude that, in view of the brief action of mephenesin elixir, its major benefit to the multiple sclerosis patient, in whom it produces usable relaxation, would seem to be in facilitating the application of physical therapy treatment. Most investigators apparently view the drug as having limited therapeutic usefulness.

Prenderol^{R} (2,2-diethyl-1,3-propanediol), a compound chemically related closely to mephenesin, has been suggested for use in many neuromuscular disorders. However, no comprehensive clinical report of its efficacy in the treatment of multiple sclerosis has been published.

MKO2, an experimental preparation of Merck, which is a combination of an atropine nucleus and an antihistamine, has been studied in 20 patients afflicted by Parkinsonism and, according to report, shows great promise of usefulness in the control of rigidity, cramps, spasm, and tension.[48] The drug, it is to be anticipated, will be used in treating multiple sclerosis patients. Judgment as to its effectiveness must be deferred for the present in the absence of specific information regarding its use in multiple sclerosis.

Agents directed toward the relief of miscellaneous symptoms. A number of agents have been reported to be of value in improving bladder function when applied to the patient suffering from multiple sclerosis. Muellner, Loman, and Alexander[49] advocate the judicious use of atropine, amphetamine sulfate, or similarly acting drugs. They claim that urecholine, combined with temporary catheter drainage of the bladder, are of value in restoring detrusor function after occasional attacks of urinary retention.

Banthine^{R}[50, 51] has been utilized as palliative treatment of neurogenic enuresis, in that it appears capable of increasing bladder capacity. This agent, although producing minimal effects, often proves to be of significant therapeutic importance to the patient.

Jonez[52] has employed a combination of d-desoxyephedrine and acetylbromdiethylacetylcarbamid (Euphased^{R}) as a palliative measure and believes it is the best antidepressant sedative now available. He found it useful also in controlling tremor. His report is brief and his criteria of improvement are not fully discussed. Acceptance for the use of the drug must therefore await confirmation of his results.

Conclusions

As yet no verified specific therapeutic agent or approach appears to have been developed which can be looked upon as a cure for multiple sclerosis.

Many of the reports claiming excellent results have not been formulated in a scientifically sound manner. Criteria of improvement or delineations from the fluctuations to be anticipated in the natural course of the illness are frequently inadequately presented. Often, benefits of therapy are ascribed to the drug or therapy under investigation. No attempt is usually made to evaluate the psychotherapeutic implications of the increased interest in, and attention given to, the patients. The problem of patient motivation is rarely considered. Many of the reported successes have not been confirmed by other investigators. Essentially the same problems exist in evaluating reports of the usefulness of the various agents used symptomatically.

Nevertheless, even though there is now no acknowledged specific treatment for multiple sclerosis itself, it must be recognized that these patients, as individuals, require symptomatic and supportive treatment, and that such treatment may frequently be of significant benefit. The program for each patient must be a highly individualized one and it must include, in addition to the comprehensive basic medical management, recognition of the patient's psychotherapeutic needs and the exploitation of established rehabilitation procedures.

Therapeutic nihilism is not only unwarranted but frequently proves to be a disservice to the patient in that it relegates his care to the cure merchant, the quasi-professional practitioner, or the cultist. The therapeutic goals must always remain realistic, however, and these goals often prove to be minimal ones, requiring skilled management by the responsible physician.

Summary

Despite common recognition of the difficulties inherent in evaluating the effects of therapy for patients afflicted by multiple sclerosis, whether directed as a hypothecated etiologic factor or for symptomatic relief, the pressure from the patient and his family for treatment has understandably persisted. Continued research and clinical efforts have been directed toward the ultimate goal of a more successful treatment, and a large number of pharmacological agents have been investigated. Experiences with many of the more recently available substances are critically reviewed and discussed in detail.

As yet no verified specific therapeutic agent or approach appears to have been developed which can be looked upon as a cure. Nevertheless, even though there is not acknowledged specific treatment for multiple sclerosis itself, it must be recognized that patients afflicted by this malady, as individuals, require symptomatic and supportive treatment, and that such treatment may frequently be of significant benefit. Therapeutic nihilism is unwarranted. The goals, however, must be realistic and require skilled management by the responsible physician.

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PSYCHOLOGICAL FACTORS IN MULTIPLE SCLEROSIS

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I think that perhaps this title, which was allotted to me some time ago, should be amplified. This paper will deal with the role of psychology, or the psychologist, in understanding the psychological problems in multiple sclerosis and in the life-situation of any individual sufferer from the disease. The title as it stands, is apt, I think, to be associated with those studies which have attempted to isolate characteristic psychological traits which occur with greater frequency in a group of multiple sclerotic patients than in some other disease entity.

The field of clinical psychology is relatively new. Because of various pressures and needs in the community, and because of the emergence of new tools for appraising and understanding personality, the clinical psychologist as a professional individual, equipped with diagnostic and re-educational (or readjustment) techniques, has appeared on the scene. In contrast to the *academic* psychologist, who is concerned with the theoretical implications of behavior, and the *experimentalist*, who deals with those problems which can be legitimately subjected to rigorous scientific conditions, the clinical psychologist offers his services in the study of the problems of any specific individual. His training is three-fold: (1) in experimental methods and procedures; (2) in diagnostic techniques, and (3) in various areas of therapeutic work. This training makes him available for various types of collaboration with his medical colleagues in dealing with the problems of multiple sclerosis.

Let me outline briefly how the clinical psychologist may function in each of these areas.

The psychologist's role as a *psychodiagnostician* has grown up around his collaboration with his *psychiatric* colleagues. During World War II, the team of psychiatrist, psychologist, and social worker did much to establish this now generally accepted position. By a battery of tests for personality appraisal, the psychologist can supplement psychiatric diagnoses with material from a slightly different angle: the depth of the emotional disturbance, its seriousness, the prevailing dynamic picture, and the patient's potential assets. It is clear that, in considering the best treatment for an emotionally disturbed patient, information of this kind has a direct and relevant bearing.

What is less well known, and what to me seems of equal importance, is the contribution of a psychological appraisal for patients whose disturbance is not essentially a psychiatric, neurotic, or emotional one, but one which follows in the wake of physical illness. It is my contention that were the techniques of the psychologist better understood the general practitioner, internist, or pediatrician would find this type of collaboration equally pertinent to problems which he handles as if they were psychiatric ones. A patient afflicted by multiple sclerosis can be better understood as a total person, it seems to me, if comparable information with reference to his particular psychodynamic equilibrium or disequilibrium is available to his physician.

If you contrast charts 1 and 2 you will see that the medical problem in the handling of these two individuals must differ to a considerable degree. The psychologist, then, in his role of psychodiagnostician may play an active part in assessing the personality problems of individual patients having multiple sclerosis.

Summary of Individual with Good Psychological Potential

Manner During Test

Overtly distressed	Uneasy	[✓ Relaxed, interested]	Competitive and tense	Hostile

Rate of Performance

Very slow	Slow	Average	[✓ Speedy]	Excessively speedy

I.Q. (Bellevue-Wechsler)

Below average	Average	High average	Superior	[✓ Very superior]

Productivity (Rorschach)

Meagre	Average	[✓ Rich and well ordered]	Rich, but chaotic	Chaotic

Relation to Reality (Rorschach, Bellevue Wechsler, Drawings)

Fanatical exactitude	Not noticeably disturbed	[✓ Firm and good]	"Artistic leeway"	Loose

Usual—Unusual Thought Content (Rorschach, Unpleasant Concept)

Stereotyped	Average	[✓ Original]	Bizarre qualities offset by other features	Bizarre

Emotional Tone (Rorschach, Szondi)

Lacking, repressed	Struggling for expression	[✓ Warm, readily available]	Getting out of hand	Emotions rampant

Constructive Fantasy (Rorschach)

Absent	Average	[✓ Active]	Active +	Topheavy, withdrawal

Passivity—Aggression (Rorschach, Szondi, Unpleasant Concept)

Hampering passivity	Insufficient drive	[✓ Sufficient drive]	Aggression +	Overpowering aggression

Chart 1

SUMMARY OF INDIVIDUAL WITH POOR PSYCHOLOGICAL POTENTIAL

Manner During Test	Overtly distressed	Uneasy	Relaxed, interested	Competitive and tense	Hostile
Rate of Performance	Very slow	Slow	Average	Speedy	Excessively speedy
I.Q. (Bellevue-Wechsler)	Below average	Average	High average	Superior	Very superior
Productivity (Rorschach)	Meagre	Average	Rich and well ordered	Rich, but chaotic	Chaotic
Relation to Reality (Rorschach, Bellevue Wechsler, Drawings)	Fanatical exactitude	Not noticeably disturbed	Firm and good	"Artistic leeway"	Loose
Usual—Unusual Thought Content (Rorschach, Unpleasant Concept)	Stereotyped	Average	Original	Bizarre qualities offset by other features	Bizarre
Emotional Tone (Rorschach, Szondi)	Lacking, repressed	Struggling for expression	Warm, readily available	Getting out of hand	Emotions rampant
Constructive Fantasy (Rorschach)	Absent	Average	Active	Active +	Topheavy, withdrawal
Passivity—Aggression (Rorschach, Szondi, Unpleasant Concept)	Hampering passivity	Insufficient drive	Sufficient drive	Aggression +	Overpowering aggression

CHART 2

Passing now to the psychologist in his *experimental* capacity, I may briefly review a study recently made by Doctor Kraus and myself which, although published, may be taken as an example of research into group characteristics or research for traits more commonly found amongst a group of multiple sclerotic patients than among others.

Harrower and Kraus recently administered a battery of psychological tests to 140 patients afflicted by multiple sclerosis and a comparable battery of tests to five independent groups of controls. These controls included 200 patients having emotional disturbances, 258 "normal" individuals or persons without overt psychological or somatic disturbances, 29 parkinsonian patients, and 21 polio patients. This study followed a previous pilot study in which we had found that while no typical, stereotyped, or uniform personality picture of the patients having multiple sclerosis emerged (such as had been found by investigators in cases of brain damage), nonetheless, in every test used, there were some items which differentiated the multiple sclerotic group from the controls. These findings, in general terms, could be epitomized as showing in the multiple sclerotic patients an overemphasis on dependency needs, a virtually complete absence of body-centered anxiety, a minimum of inner conflict, or an attitude of resignation and unrealistic tendency to see the world as through colored glasses. We felt that it was important to emphasize that the discovery of certain trends in the group as a whole did not mean that every patient in the multiple sclerotic group showed these characteristics. It was only that the incidence of these traits was significantly higher in this group than in the control group. Individual multiple sclerotic patients deviated markedly from the general pattern, some giving no indications of the characteristic constellation of the findings.

Our large-scale study reinforced the findings of the initial one. Those same traits, particularly those of overdependency and an unrealistic absence of body-centered anxiety, were as strongly evidenced as before. A breakdown of our multiple sclerotic group into cases during remission, cases which were mild, and cases which were advanced, showed certain distinct group characteristics.

Characteristic of the patients in remission was a higher percentage of persons having superior intelligence and the lowest amount of erratic performance. We also found that, on the personality test, they showed a capacity for richer psychological experience in living. There was the highest percentage of expanded personality types; a further characteristic could be described as a more realistic willingness to allow the anxiety component to register, as such, in consciousness. Here one could raise the perplexing question: do these so-called better personality characteristics allow for remissions to take place, or are they the result of changes in the disease process?

Among the patients afflicted by mild, early forms of the disease was found the greatest amount of overt distress as regards the experience of the illness itself. One could say that the amount of anxiety related to the disease was in inverse proportion to the extent to which the patient was seriously handicapped at the time of the examination.

We also found that in the specific environment of the Kaiser-Kabat Institute, where multiple sclerosis patients were encouraged to be as independent as possible, the so-called dependency scores were higher among those patients examined immediately on arrival than in those who had been exposed to the "treatment." The former also showed quite a shift towards extrovertial living as reflected in the Rorschach Test.

As a result of these findings, we were left with a feeling that the psychological characteristics could not be considered as predisposing the person to the disease. Rather that the disease imposed certain standard conditions on the individual patient, leaving its mark to a greater or lesser degree, depending on the patient's premorbid personality structure. When living conditions were changed, changes were reflected in the test score.

Let us now consider the psychologist in his capacity of *re-educator* or his role in the whole therapeutic picture. While it must be stated that there is considerable controversy in the medical and psychological professions as to the psychologist's status as an independent therapist there is, I think, no disagreement whatsoever to the fact that within a medical framework, or as a part of a medical team, the psychologist may function in a therapeutic capacity. It is further unquestioned that where major personality changes are not attempted, or where it is essentially a matter of counseling or guidance, the psychologist in this capacity could be called in without hesitation.

To the great credit, it seems to me, of those who direct and plan work in the field of multiple sclerosis, this active use of psychotherapeutic techniques within the general clinical picture has been recognized for some time. The important group therapy work which is being done under the guidance of Doctor Alexander in Boston points the way to major contributions in this field. Those of us who have worked actively in a counseling or therapeutic capacity with patients suffering from multiple sclerosis have seen the extent to which the adjustment of acute personal problems may contribute not so much to the disease per se, but to the functioning of that individual in a less self-destructive and more creative manner. If research funds were available, an important piece of quantitative work to be done would be the systematic and careful contrasting of a group of patients exposed to psychotherapy as opposed to a matched group who received no such help.

There is a fourth area in which it seems to me the clinical psychologist can function. I have recently completed a series of interviews with multiple sclerotic patients to determine the things which bother them most about their disease, in order to write a little psychotherapy for the patient's use. Briefly, it was possible for me to make explicit several very vague and undifferentiated areas of anxiety that recurred frequently, though in slightly different form, among many patients. Over and above specific personality problems which were naturally individualized, and over and above the specific life-situation problems which varied to some extent for each patient, and over and above the specific traits which emerged as more common in the multiple sclerotic group than in other disease entities, there were found certain problems relating to (1) the *variability* of symptoms in multiple sclerosis, (2) to the *uncertainty* of remission or acceleration of the disease process, and (3) to the *loss of control* over various bodily functions. These problems and others like them might truly be called the psychological problems of multiple sclerosis and as such, available for scrutiny by the psychologist. In conclusion, allow me to express the hope that, since all suffering has a large psychological component in it, many people will be drawn from the ranks of psychologists to help those afflicted by multiple sclerosis.

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